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ORIGINAL RESEARCH

The Feelings About genomiC Testing Results (FACToR) Questionnaire: Development and Preliminary Validation

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Abstract

The purpose of this study was to develop a brief instrument, the Feelings About genomiC Testing Results (FACToR), to measure the psychosocial impact of returning genomic findings to patients in research and clinical practice. To create the FACToR, we modified and augmented the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire based on findings from a literature review, two focus groups ($N = 12$), and cognitive interviews ($N = 6$). We evaluated data from 122 participants referred for evaluation for inherited colorectal cancer or polyposis from the New EXome Technology in (NEXT) Medicine Study, an RCT of exome sequencing versus usual care. We assessed floor and ceiling effects of each item, conducted principal component analysis to identify subscales, and evaluated each subscale's internal consistency, test-retest reliability, and construct validity. After excluding items that were ambiguous or demonstrated floor or ceiling effects, 12 items forming four distinct subscales were retained for further analysis: negative emotions, positive feelings, uncertainty, and privacy concerns. All four showed good internal consistency (0.66–0.78) and test-retest reliability (0.65–0.91). The positive feelings and the uncertainty subscales demonstrated known-group validity. The 12-item FACToR with four subscales shows promising psychometric properties on preliminary evaluation in a limited sample and needs to be evaluated in other populations.

Keywords Genomic testing · Psychological impact · Instrument development and validation · Colorectal cancer

Introduction

As of July 2017, genomic tests are available from over 700 laboratories in the USA for over 5000 disorders ("GeneTests," 2017). Information from genomic tests is potentially valuable for decision-making about disease surveillance and prevention, early detection, and treatment (NIH Research Portfolio Online Reporting Tools (RePORT) 2013). For example, individuals who inherit alterations in major colorectal cancer susceptibility genes have approximately a 50–100% lifetime risk

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of developing colorectal cancer (Gryfe 2009). However, the utility of genomic tests and sequencing in clinical care has raised a variety of concerns about the potential psychological effects of such results on both patients and their family members who might also be at risk. Evidence thus far on the psychological consequences of acquiring genetic information is inconclusive. A meta-analysis found that among participants undergoing predictive genetic testing for BRCA1/2 mutations, distress among carriers increased shortly after receiving results and returned to pre-testing level over time, while distress among non-carriers and those with inconclusive results decreased over time (Hamilton et al. 2009). A systematic review of genetic testing for Huntington's disease, hereditary breast and ovarian cancer, familial adenomatous polyposis and spinocerebellar ataxia found that both carriers and non-carriers showed decreased distress after testing, with greater and more rapid decrease among non-carriers (Broadstock et al. 2000). A recent systematic review in Huntington's disease found no association between genetic test result and psychological impact and there were fluctuations in levels of distress for carriers and non-carriers alike (Crozier et al. 2014). In children, serious adverse psychological outcomes were uncommon (Wakefield et al. 2016). Most studies reported no significant increase in anxiety, depression, or distress among carriers, while some reported intrafamilial distress, discrimination, and guilt/regret (Wakefield et al. 2016). Additionally, there are oftentimes concerns about discrimination in employment and access to health insurance, especially when the inherent identifiability of genomic information is considered (Apse et al. 2004; Bombard et al. 2009; Penziner et al. 2008).

As clinical genomics progresses, it is important to understand the psychological consequences for patients receiving genomic test results in a variety of clinical settings. Two instruments have been developed and validated specifically for genomic testing: the Psychological Adaptation to Genetic Information Scale (PAGIS) and the Multidimensional Impact of Cancer Risk Assessment (MICRA) (Cella et al. 2002; Read et al. 2005). The PAGIS was developed to assess the psychological impact of genomic testing in a wide range of conditions (Read et al. 2005). It has 26 items and five subscales: non-intrusiveness, support, self-worth, certainty, and self-efficacy (Read et al. 2005). The initial items were generated from a literature review and a focus group of the staff of a genetics clinic and one parent of a child with a genetic condition (Read et al. 2005). The scale was then validated in a sample where 4% of all 323 respondents learned about disease risk through genomic tests (Read et al. 2005).

The MICRA was developed to specifically assess the positive and negative psychological effects of receiving genomic test results in cancer patients. The items were constructed from a literature review and brief interviews with experts and patients (Cella et al. 2002). The final 25-item questionnaire contains 21 questions to be completed by all respondents and four questions conditional on factors such as parenthood status, test result, and cancer diagnosis (Cella et al. 2002). The MICRA was validated in a sample of 158 women with varied breast and ovarian cancer status, *BRCA1/2* status, and family history of breast cancer (Cella et al. 2002). Three subscales were identified in the validation: positive experiences, distress, and uncertainty, and the MICRA total scale and subscales were found to have good psychometric properties in the setting of high-risk cancer susceptibility (Cella et al. 2002).

In the era of patient-centered research, the very limited patient input in the construction of items has limited the content validity of PAGIS. The MICRA was developed for the specific context of genomic testing in cancer and cannot be used in other disease areas without formal adaptation and validation. Other psychosocial questionnaires commonly used in the genomic testing setting are measures of psychiatric symptoms and may lack sensitivity to the unique issues raised by genomic testing, such as uncertainty due to inconclusive test results and concerns about the implications of test results for family members. In addition to addressing these gaps, a shorter instrument was desired for incorporation alongside other assessments in genomic studies and patient care. The purpose of developing the Feelings About genomiC Testing Results (FACToR) was to design a brief, sensitive, and patient-centered instrument that can be used to measure the psychological impact of receiving genomic test results in a wide range of clinical conditions.

Materials and Methods

Sample for Analysis of Measurement Properties

Following approval from the University of Washington Institutional Review Board, the study sample for the validation of the FACToR was drawn from the NEXT (New EXome Technology in) Medicine Study, a randomized controlled trial designed to evaluate the effect of whole exome sequencing (WXS) on (1) the speed of reaching a genomic diagnosis, (2) patient burden due to genomic testing, and (3) testing costs in genetics clinics. Potential participants in the trial were identified from screening all adult patients referred for genomic evaluation for hereditary colorectal cancer and polyposis (CRCP) at the University of Washington Medical Center Genetic Medicine Clinic or the Seattle Cancer Care Alliance. Patients who were referred to the medical genetics clinic and indicated for Lynch syndrome screening were eligible for inclusion in the study. Upon completion of the baseline study visit, consented participants were randomized to either the control arm with usual care testing or the intervention arm, which included WXS and usual care testing.

During the 1-year follow-up after randomization, participants completed two clinic visits and seven surveys that

were administered either online or through postal mail, according to their preference. At the first clinic visit, participants returned to the clinic or called in to be unmasked to their randomization assignment and receive the results of their clinical CRCP genomic test. Participants randomized to the WXS arm also received CRCP-related findings from WXS at this visit. At the first clinic visit, incidental findings identified by WXS that were not related to CRCP were not returned to the participants. Two weeks after the first clinic visit, participants of both arms were sent a survey that included the Veterans RAND 12 Item Health Survey (VR-12) (Kazis et al. 1990), the Generalized Anxiety Disorder 7-Item Scale (GAD-7) (Spitzer, Kroenke, Williams, & Lo, 2006), the Brief Patient Health Questionnaire Mood Scale (PHQ-9) (Martin et al. 2006), a five-item version of the Mental Health Inventory (MHI-5) (Berwick et al. 1991), one question on satisfaction with genomic testing, a survey on preferences for genomic testing, and the FACToR. Two weeks after completing the first survey, the last 30 participants enrolled were asked to complete the FACToR again for the evaluation of the instrument's test-retest reliability. We used data from the surveys 2 weeks after the first clinic visit and data from the 30 participants who completed the FACToR again 2 weeks after to assess the psychometric properties of the FACToR. Since the FACToR (and the MICRA) specifically refer to the impact of genetic test results, a pre/post comparison design was not possible.

Preliminary Item Pool

The preliminary item pool of the FACToR was derived from the MICRA (Cella et al. 2002). We reviewed existing instruments that focus specifically on psychological responses to genomic information in any disease area and identified the MICRA as one of the most commonly used. One of the strengths of the MICRA is its ability to examine the impact of specific information and more nuanced outcomes. Although the MICRA was developed specifically for cancer genomic testing, many of its items are potentially relevant for genomic testing beyond cancer. Furthermore, the MICRA's development process included an adequate sample of patients from the target population in their concept elicitation, which provided evidence for the content validity of the instrument. Lastly, modifications of the MICRA were most commonly used in the Clinical Sequencing Exploratory Research (CSER) consortium of which this project is a part (Gray et al. 2014). We followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines on content validity in eliciting concepts in focus groups and assessing respondent understanding in cognitive interviews (Patrick et al., 2011, 2011).

Focus Groups

We conducted two focus groups among patients who had been tested for a hereditary colorectal cancer predisposition at the University of Washington Genetic Medicine Clinic. The goal of conducting these focus groups was not to reach complete saturation of concepts, but to identify additional salient concepts not covered by the MICRA. We recruited individuals both *with* and *without* colorectal cancer and those who received a positive, negative, or inconclusive result from a genomic test to maximize variation in testing experience. In total, 12 individuals participated in one of the two focus groups with one consisting of individuals who obtained an informative genomic test result and the other of individuals who obtained an uninformative result. Two experienced qualitative researchers led the focus groups and explored participants' perceptions of genomic tests. From the results of these focus groups, we added two items, concern that genomic testing would affect employment and positive experience from improved ability to plan for the future. We deleted MICRA item #9 "Worrying about my risk of getting cancer [or getting cancer again if you have ever been diagnosed with cancer]," as this question may not apply to areas other than prognostic genomic tests. Detailed descriptions of the methods and results of the focus groups are available in the Online Appendix.

Cognitive Interviews

We conducted six semi-structured cognitive interviews with "think-aloud" and "probing" techniques to refine the language and further assess the comprehensiveness and relevance of the instrument's content relative to the patients' experience. Similar to the focus group sample and the validation sample, the cognitive interview sample was recruited at the University of Washington Genetic Medicine Clinic. Patients interviewed ranged in age, cancer status, and type of genomic test results. The cognitive interviews informed several substantive changes to the items. First, we replaced "cancer" with "disease" to make the questions applicable in not only cancer populations but also individuals with other diseases. Second, we rephrased the items as questions to improve comprehensiveness. Third, we changed the responses from frequency to intensity to measure impact and better align with patients' experience. Fourth, we increased the number of response categories from four to five to allow for greater variation in responses. Lastly, we changed each occurrence of "test result" to "genetic test result" to be more specific. We also probed for redundancies in the questions but did not identify any question that clearly warranted deletion. Detailed descriptions of the methods and results of the cognitive interviews are available in the Online Appendix.

By the end of the development process, the preliminary item pool for the FACToR consisted of 26 items (Tables 2

and 3). Items 1–18 apply to all respondents; items 19–22 apply to only those who have discussed their genomic test results with their family members; items 23 and 24 apply only to those who have children; items 25 and 26 apply only to those who have been diagnosed with cancer. Respondents are asked to indicate how much they had each specific feeling in the past week by circling one answer for each question: not at all (0), a little (1), somewhat (2), a good deal (3), or a great deal (4).

Measures

The VR-12, the GAD-7, the PHQ-9, and the MHI-5 were administered as construct validation measures alongside the FACToR in the NEXT Medicine Study. These scales were selected because they were the standard and widely used tests of anxiety and depression and have been used in the context of genomic testing. The VR-12 is one of the most commonly used health-related quality of life instruments (Kazis et al., 1990). It has 12 items that comprise two scales: role limitations due to physical problems and role limitations due to emotional problems (Kazis et al., 2004). Scores on either scale can be standardized so that it ranges from 0 to 100, with a higher score indicating better health and a mean score of 50 for the U.S. general population (Selim et al., 2009).

The GAD-7 is a 7-item anxiety scale that identifies probable cases of generalized anxiety disorder (GAD) and assesses its severity (Spitzer et al., 2006). A total score, ranging from 0 to 21, is calculated by summing scores from individual items. A higher total score indicates greater severity of anxiety (Spitzer et al., 2006). A cut point of 10 or greater on the GAD-7 has high sensitivity and specificity in identifying cases of GAD (Spitzer et al., 2006). Cut points of 5, 10, and 15 can be interpreted as representing mild, moderate, and severe levels of anxiety on the GAD-7 (Spitzer et al., 2006).

The PHQ-9 is a 9-item mood scale that identifies probable cases of major depression and measures its severity (Kroenke et al., 2001). A total score, ranging from 0 to 27, is calculated by adding scores from individual items; a higher total score indicates greater severity of depression (Kroenke et al., 2001). A cut point of 10 or greater on the PHQ-9 has high sensitivity and specificity for identifying major depression (Kroenke et al., 2001). Cut points of 5, 10, 15, and 20 can be interpreted as representing mild, moderate, moderately severe, and severe depression, respectively (Kroenke et al., 2001).

The MHI-5 is the 5-item mental health scale of SF-36® (Ware & Gandek, 1998). A total score is calculated by summing scores from items that ask about negative feelings and reversed scores from items that ask about positive feelings. The total score is then often transformed into a value ranging from 0 to 100 using a linear transformation. Therefore, a higher score on the MHI-5 indicates worse mental health. The scale was not originally developed with cut points for mental health disorders; however, subsequent studies have suggested that a cut point of 76 or greater can be used to identify common mental disorders (Berwick et al., 1991; Kelly et al., 2008; Rumpf et al., 2001).

Statistical Analysis

Descriptive statistics (i.e., frequencies, means, standard deviations [SD], and 95% confidence intervals [CI]) were used to summarize the sociodemographic characteristics, CRCP history, and baseline functioning of the participants of the validation study. Descriptive statistics of item-level responses were used to evaluate evidence of floor or ceiling effects ($\geq$ 85% respondents choosing the lowest or the highest response category) as well as missing data. Principal component analysis (PCA) with varimax rotation was conducted to extract subscales from the FACToR items. Cronbach's α coefficient was calculated to assess the internal consistency of each subscale of the FACToR. One-way ANOVA was used to evaluate the known-group validity (discriminant validity based on characteristics of the respondents or some known group) of each subscale. Pearson's correlation coefficients between the FACToR's subscale scores and scores from the other mental health instruments administered in the trial were calculated to assess the construct validity. Intraclass correlation coefficients (ICCs) were calculated to evaluate the test-retest reliability of each subscale. Items that measure positive feelings were reversely scored in the analyses of reliability and validity so that a higher score indicated greater impairment. All statistical analyses were conducted in R (Version 3.4.0).

We hypothesized that the FACToR items can be grouped into similar subscales as the MICRA: positive experiences/feelings, distress/negative emotions, and uncertainty. In addition, the two items on the concerns for health insurance status and employment status would form a distinct subscale that measures privacy concerns. We further hypothesized that the FACToR subscales that measure positive feelings and negative emotions would be weakly correlated with generic measures of anxiety and depression, as generic measures might not be sensitive enough in this specific context, while the subscales that measure uncertainty and privacy concerns would not.

Results

Validation Sample

Table 1 presents the sociodemographic characteristics, colorectal cancer history, and baseline functioning of the participants in the validation sample. The mean age of the study population was 53.4 years (SD: 13.2). Fifty-eight percent of the study sample were male. The majority were white,

Table 1 Sociodemographic characteristics, colorectal cancer history, and functioning of study participants at baseline ($N = 122$)

Variable	Negative ($n = 85$)	Positive ($n = 12$)	VUS ($n = 25$)	Overall ($N = 122$)	P value[a]
Age, mean (SD)	52.8 (13.4)	56.3 (9.4)	54.2 (14.2)	53.4 (13.2)	0.544
Male, *N* (%)	43 (50.6)	5 (41.7)	10 (40.0)	58 (47.5)	0.591
White, *N* (%)	69 (81.2)	9 (75.0)	20 (80.0)	98 (80.3)	0.240
Marital status, *N* (%)					0.329
Now married	59 (69.4)	11 (91.7)	16 (64.0)	86 (70.5)	
Living with a partner	6 (7.1)	0 (0)	0 (0)	6 (4.9)	
Widowed	1 (1.2)	0 (0)	1 (4.0)	2 (1.6)	
Divorced	10 (11.8)	0 (0)	2 (8.0)	12 (9.8)	
Never married	9 (10.6)	1 (8.3)	6 (24.0)	16 (13.1)	
Have children, *N* (%)	63 (75.0)	11 (91.7)	16 (64.0)	90 (73.8)	0.264
Education, *N* (%)					0.123
Did not graduate high school	1 (1.2)	0 (0)	0 (0)	1 (0.8)	
High school graduate	9 (10.6)	1 (8.3)	2 (8.0)	12 (9.8)	
Completed vocational/trade school	6 (7.1)	0 (0)	1 (4.0)	7 (5.7)	
Some college	17 (20.0)	7 (58.3)	3 (12.0)	27 (22.1)	
College degree	35 (41.2)	1 (8.3)	10 (40.0)	46 (37.7)	
Graduate degree	17 (20.0)	3 (25.0)	9 (36.0)	29 (23.8)	
Employed, *N* (%)	55 (64.7)	8 (66.7)	16 (64.0)	79 (64.8)	0.920
Income, *N* (%)					0.568
Less than $25,000	8 (9.4)	1 (8.3)	3 (12.0)	12 (9.8)	
$25,000–$50,000	9 (10.6)	1 (8.3)	5 (20.0)	15 (12.3)	
$51,000–$100,000	28 (32.9)	2 (16.7)	8 (32.0)	38 (31.1)	
Over $100,000	33 (38.8)	8 (66.7)	7 (28.0)	48 (39.3)	
Have been diagnosed with colorectal cancer, *N* (%)	30 (35.3)	6 (50.0)	8 (32.0)	44 (36.1)	0.803
Have health insurance, *N* (%)	74 (87.1)	9 (75.0)	20 (80.0)	103 (84.4)	0.475
VR-12					
Physical Component Score	45.2 (12.5)	46.1 (13.7)	48.5 (12.6)	45.9 (12.6)	0.276
Mental Component Score	51.4 (7.9)	49.1 (11.7)	48.8 (8.5)	50.6 (8.5)	0.155
GAD-7 total score	3.2 (4.0)	3.4 (4.2)	4.9 (4.0)	3.6 (4.1)	0.102
PHQ-9 total score	3.9 (4.2)	3.7 (4.7)	4.2 (3.3)	3.9 (4.1)	0.843
MHI-5 total score	79.2 (15.0)	74.1 (22.2)	72.3 (15.3)	77.3 (16.0)	0.057

[a] P values from one-way ANOVA for continuous variables and chi-square tests for categorical variables

currently married, have children, college educated, employed, insured, and had an annual income higher than $50,000. Thirty-six percent had been previously diagnosed with colorectal cancer. At baseline, the study population had a mean score of 45.9 (SD: 12.6) on the VR-12 physical component, 50.6 (SD: 8.5) on the VR-12 mental component, 3.6 (SD: 4.1) on the GAD-7, 3.9 (SD: 4.1) on the PHQ-9, and 77.3 (SD: 16.0) on the MHI-5.

At the first clinic visit, 12 (10%) participants received a test result from either usual care test or whole exome sequencing test that indicated a pathogenic or likely pathogenic variant (positive), 25 (20%) received a test result that indicated a Variant of Unknown Significance (VUS, an inconclusive result), while 85 (70%) received a result that did not indicate either type of variant (negative). Baseline characteristics did not differ significantly between participants receiving different types of genomic findings.

Data Quality

In the evaluation of distributions of responses, seven items demonstrated floor or ceiling effect in either the positive or the VUS group (Table 2, Table 3): *#4*, #6, *#7*, *#12*, *#14*, *#16*, and *#18*. Among these, item #18 was retained because concern about employment was shown to be an important concept in the focus groups and cognitive interviews. Item #6 was also retained so that there would be at least three questions that measure negative emotions. Item #11 was excluded because such difficulty could be due to negative emotions, a lack of information regarding screening and prevention, or concerns

Table 2 Item-level responses by genomic test finding to assess floor/ceiling effect ($N = 122$)

Item	Level[a]	Negative ($n = 85$), n (%)	Positive ($n = 12$), n (%)	VUS ($n = 25$), n (%)	Overall ($N = 122$), n (%)	P value[b]
1. How upset did you feel about your genetic test result?	0	79 (92.9)	8 (66.7)	18 (72.0)	105 (86.1)	0.019
	1	3 (3.5)	2 (16.7)	5 (20.0)	10 (8.2)	
	2	1 (1.2)	1 (8.3)	2 (8.0)	4 (3.3)	
	3	2 (2.4)	1 (8.3)	0 (0)	3 (2.5)	
	4	0 (0)	0 (0)	0 (0)	0 (0)	
2. How happy did you feel about your genetic test result?	0	7 (8.2)	7 (58.3)	5 (20.0)	19 (15.6)	< 0.001
	1	4 (4.7)	2 (16.7)	0 (0)	6 (4.9)	
	2	18 (21.2)	1 (8.3)	11 (44.0)	30 (24.6)	
	3	27 (31.8)	2 (16.7)	4 (16.0)	33 (27.0)	
	4	29 (34.1)	0 (0)	5 (20.0)	34 (27.9)	
3. How anxious or nervous did you feel about your genetic test result?	0	66 (77.6)	8 (66.7)	19 (76.0)	93 (76.2)	0.791
	1	12 (14.1)	2 (16.7)	4 (16.0)	18 (14.8)	
	2	5 (5.9)	1 (8.3)	2 (8.0)	8 (6.6)	
	3	1 (1.2)	1 (8.3)	0 (0)	2 (1.6)	
	4	1 (1.2)	0 (0)	0 (0)	1 (0.8)	
4. How guilty did you feel about your genetic test result?	0	79 (92.9)	9 (75.0)	23 (92.0)	111 (91.0)	0.318
	1	3 (3.5)	1 (8.3)	1 (4.0)	5 (4.1)	
	2	3 (3.5)	2 (16.7)	1 (4.0)	6 (4.9)	
	3	0 (0)	0 (0)	0 (0)	0 (0)	
	4	0 (0)	0 (0)	0 (0)	0 (0)	
5. How relieved did you feel about your genetic test result?	0	10 (11.8)	3 (25.0)	5 (20.0)	18 (14.8)	0.002
	1	7 (8.2)	6 (50.0)	5 (20.0)	18 (14.8)	
	2	19 (22.4)	2 (16.7)	8 (32.0)	29 (23.8)	
	3	19 (22.4)	1 (8.3)	3 (12.0)	23 (18.9)	
	4	30 (35.3)	0 (0)	4 (16.0)	34 (27.9)	
6. How sad did you feel about your genetic test result?	0	81 (95.3)	9 (75.0)	22 (88.0)	112 (91.8)	0.106
	1	2 (2.4)	2 (16.7)	2 (8.0)	6 (4.9)	
	2	1 (1.2)	0 (0)	1 (4.0)	2 (1.6)	
	3	1 (1.2)	1 (8.3)	0 (0)	2 (1.6)	
	4	0 (0)	0 (0)	0 (0)	0 (0)	
7. How much loss of control over your life did you feel because of your genetic test result?	0	81 (95.3)	9 (75.0)	24 (96.0)	114 (93.4)	0.004
	1	2 (2.4)	3 (25.0)	0 (0)	5 (4.1)	
	2	2 (2.4)	0 (0)	1 (4.0)	3 (2.5)	
	3	0 (0)	0 (0)	0 (0)	0 (0)	
	4	0 (0)	0 (0)	0 (0)	0 (0)	
8. How frustrated did you feel that there are no definite disease prevention guidelines for you?	0	56 (65.9)	5 (41.7)	17 (68.0)	78 (63.9)	0.502
	1	20 (23.5)	5 (41.7)	5 (20.0)	30 (24.6)	
	2	7 (8.2)	1 (8.3)	3 (12.0)	11 (9.0)	
	3	2 (2.4)	1 (8.3)	0 (0)	3 (2.5)	
	4	0 (0)	0 (0)	0 (0)	0 (0)	
9. How uncertain did you feel about what your genetic test result means for you?	0	56 (65.9)	5 (41.7)	14 (56.0)	75 (61.5)	0.027
	1	22 (25.9)	3 (25.0)	5 (20.0)	30 (24.6)	
	2	3 (3.5)	4 (33.3)	3 (12.0)	10 (8.2)	
	3	3 (3.5)	0 (0)	3 (12.0)	6 (4.9)	
	4	1 (1.2)	0 (0)	0 (0)	1 (0.8)	
10. How uncertain did you feel about what your genetic test result means	0	51 (60.0)	2 (16.7)	12 (48.0)	65 (53.3)	0.016
	1	20 (23.5)	4 (33.3)	5 (20.0)	29 (23.8)	
	2	8 (9.4)	3 (25.0)	4 (16.0)	15 (12.3)	

Table 2 (continued)

Item	Level[a]	Negative ($n = 85$), n (%)	Positive ($n = 12$), n (%)	VUS ($n = 25$), n (%)	Overall ($N = 122$), n (%)	P value[b]
for your child(ren) and/or family's risk of disease?	3	2 (2.4)	0 (0)	3 (12.0)	5 (4.1)	
	4	4 (4.7)	3 (25.0)	1 (4.0)	8 (6.6)	
11. How much difficulty did you have making decisions about getting disease screening or doing anything to prevent disease?	0	79 (92.9)	10 (83.3)	21 (84.0)	110 (90.2)	0.143
	1	1 (1.2)	0 (0)	3 (12.0)	4 (3.3)	
	2	3 (3.5)	2 (16.7)	1 (4.0)	6 (4.9)	
	3	1 (1.2)	0 (0)	0 (0)	1 (0.8)	
	4	1 (1.2)	0 (0)	0 (0)	1 (0.8)	
12. How much did you experience problems enjoying life because of your genetic test result?	0	79 (92.9)	8 (66.7)	25 (100.0)	112 (91.8)	0.019
	1	3 (3.5)	3 (25.0)	0 (0)	6 (4.9)	
	2	2 (2.4)	1 (8.3)	0 (0)	3 (2.5)	
	3	1 (1.2)	0 (0)	0 (0)	1 (0.8)	
	4	0 (0)	0 (0)	0 (0)	0 (0)	
13. How much did you feel that you understood clearly your choices for disease prevention or early detection?	0	7 (8.2)	2 (16.7)	4 (16.0)	13 (10.7)	0.195
	1	9 (10.6)	3 (25.0)	6 (24.0)	18 (14.8)	
	2	20 (23.5)	1 (8.3)	4 (16.0)	25 (20.5)	
	3	19 (22.4)	5 (41.7)	5 (20.0)	29 (23.8)	
	4	30 (35.3)	1 (8.3)	6 (24.0)	37 (30.3)	
14. How much do you feel that the genetic test result affected your work or family life?	0	72 (84.7)	9 (75.0)	22 (88.0)	103 (84.4)	0.145
	1	8 (9.4)	1 (8.3)	2 (8.0)	11 (9.0)	
	2	3 (3.5)	0 (0)	1 (4.0)	4 (3.3)	
	3	0 (0)	1 (8.3)	0 (0)	1 (0.8)	
	4	2 (2.4)	1 (8.3)	0 (0)	3 (2.5)	
15. How concerned did you feel that your genetic test result would affect your health insurance status?	0	64 (75.3)	8 (66.7)	21 (84.0)	93 (76.2)	0.696
	1	9 (10.6)	3 (25.0)	2 (8.0)	14 (11.5)	
	2	6 (7.1)	0 (0)	1 (4.0)	7 (5.7)	
	3	3 (3.5)	0 (0)	0 (0)	3 (2.5)	
	4	3 (3.5)	1 (8.3)	1 (4.0)	5 (4.1)	
16. How much regret did you feel about the decision to receive a genetic test?	0	83 (97.6)	11 (91.7)	23 (92.0)	117 (95.9)	0.110
	1	2 (2.4)	0 (0)	0 (0)	2 (1.6)	
	2	0 (0)	1 (8.3)	1 (4.0)	2 (1.6)	
	3	0 (0)	0 (0)	1 (4.0)	1 (0.8)	
	4	0 (0)	0 (0)	0 (0)	0 (0)	
17. How helpful was the information you received from your genetic test result in planning for the future?	0	21 (24.7)	0 (0)	4 (16.0)	25 (20.5)	0.278
	1	16 (18.8)	3 (25.0)	7 (28.0)	26 (21.3)	
	2	16 (18.8)	6 (50.0)	6 (24.0)	28 (23.0)	
	3	14 (16.5)	2 (16.7)	4 (16.0)	20 (16.4)	
	4	18 (21.2)	1 (8.3)	4 (16.0)	23 (18.9)	
18. How concerned did you feel that your genetic test result would affect your employment status?	0	77 (90.6)	11 (91.7)	23 (92.0)	111 (91.0)	0.234
	1	6 (7.1)	1 (8.3)	0 (0)	7 (5.7)	
	2	0 (0)	0 (0)	1 (4.0)	1 (0.8)	
	3	2 (2.4)	0 (0)	0 (0)	2 (1.6)	
	4	0 (0)	0 (0)	1 (4.0)	1 (0.8)	

[a] Participants are asked to indicate how much they had each specific feeling in the past week by circling the one answer for each question: *not at all (0), a little (1), somewhat (2), a good deal (3), or a great deal*

[b] P values from chi-square tests for categorical variables

Table 3 Items deleted from the preliminary item pool

Items
Floor/ceiling effect
4. How guilty did you feel about your genetic test result?
7. How much loss of control over your life did you feel because of your genetic test result?
12. How much did you experience problems enjoying life because of your genetic test result?
14. How much do you feel that the genetic test result affected your work or family life?
16. How much regret did you feel about the decision to receive a genetic test?
Ambiguous
11. How much difficulty did you have making decisions about getting disease screening or doing anything to prevent disease?
14. How much do you feel that the genetic test result affected your work or family life?
Have discussed genetic test results with family
19. How much difficulty did you have talking about your genetic test results with family members?
20. How supportive do you feel that your family has been during the genetic counseling and testing process?
21. How satisfied did you feel with communication with your family about your genetic test result?
22. How worried did you feel that the genetic counseling and testing process has brought about conflict within your family?
Have children
23. How worried did you feel about the possibility of your children getting a disease?
24. How guilty did you feel about possibly passing on the disease risk to your child(ren)?
Have cancer currently or have had it in the past
25. How much do you feel your genetic test result has made it harder to cope with your cancer?
26. How much do you feel your genetic test result has made it easier to cope with your cancer?

regarding access to or coverage of disease screening and prevention. The language of item #14 was also ambiguous and can be interpreted either positively or negatively. Items #19–26, only applicable to certain subgroups of patients, were set aside from this validation. The level of missingness of the remaining 12 items (Table 4) was low: the overall missingness was approximately 5%.

Principal Component Analysis

In PCA with varimax rotation, four distinct and definable clusters of items were isolated and labeled (Table 4): negative emotions (#1, #3, and #6), positive feelings (#2, #5, #13, and #17), uncertainty (#8, #9, and #10), and privacy concerns (#15 and #18). All factor loadings were greater than 0.6 except for #3 on negative emotions (factor loading: 0.36; Table 5).

Table 4 Final items and subscales of the FACToR

Items
Negative emotions
1. How upset did you feel about your genetic test result?
3. How anxious or nervous did you feel about your genetic test result?
6. How sad did you feel about your genetic test result?
Positive feelings
2. How happy did you feel about your genetic test result?
5. How relieved did you feel about your genetic test result?
13. How much did you feel that you understood clearly your choices for disease prevention or early detection?
17. How helpful was the information you received from your genetic test result in planning for the future?
Uncertainty
8. How frustrated did you feel that there are no definite disease prevention guidelines for you?
9. How uncertain did you feel about what your genetic test result means for you?
10. How uncertain did you feel about what your genetic test result means for your child(ren) and/or family's risk of disease?
Privacy concerns
15. How concerned did you feel that your genetic test result would affect your health insurance status?
18. How concerned did you feel that your genetic test result would affect your employment status?

Participants are asked to indicate how much they had each specific feeling in the past week by circling the one answer for each question: *not at all (0), a little (1), somewhat (2), a good deal (3), or a great deal (4)*. The overall missingness of the 12-item FACToR is 5.4%

Scoring

A summary score for each subscale of the FACToR was calculated by adding scores from individual items in that subscale. For items that measure positive feelings, scores were first reversed before being summed into a total score. Therefore, the range of total score was 0–12 on the negative emotions subscale, 0–16 on the positive feelings subscale, 0–12 on the uncertainty subscale, and 0–8 on the privacy concerns subscale, all with a higher score indicating greater functional impairment.

Internal Consistency

All four subscales had good internal consistency: the Cronbach's α coefficients were 0.66 (95% CI: 0.55–0.77) for the negative emotions subscale, 0.78 (95% CI: 0.71–0.84) for the positive feelings subscale, 0.72 (95% CI: 0.64–0.8) for the uncertainty subscale, and 0.70 (95% CI: 0.61–0.79) for the privacy concerns subscale (Table 6). Established instruments that were administered alongside the FACToR in the NEXT Medicine Study also demonstrated high internal consistency in this validation study: the

Table 5 Factor structure and factor loadings after varimax rotation of 12 items in principal component analysis

Items	Components			
	1	2	3	4
1. Felt upset	0.87			
3. Felt anxious or nervous	0.36			
6. Felt sad	0.89			
2. Felt happy		0.79		
5. Felt relieved		0.84		
13. Understood choices for disease prevention or early detection		0.69		
17. Helpful in planning for the future?		0.73		
8. Felt frustrated about no definite disease prevention guidelines			0.61	
9. Felt uncertain about self			0.91	
10. Felt uncertain about family's risk of disease			0.67	
15. Felt concerned about health insurance status				0.88
18. Felt concerned about employment status				0.88

Cronbach's α was 0.93 (95% CI: 0.91–0.95) for the VR-12 physical component, 0.88 (95% CI: 0.85–0.91) for the VR-12 mental component, 0.89 (95% CI: 0.86–0.92) for the GAD-7, 0.86 (95% CI: 0.82–0.89) for the PHQ-9, and 0.88 (95% CI: 0.84–0.91) for the MHI-5.

Validity

Patients who received a positive genomic finding had the highest scores on the negative emotions subscale (mean score: 1.6; SD: 2.7), the positive feelings subscale (mean score: 10.0; SD: 2.4), and the uncertainty subscale (mean score: 3.6; SD: 2.9), followed by those who received a VUS finding (mean scores on those subscales: 0.8, 8.0, and 2.3; SDs: 1.6, 4.3, and 2.8) and those who received a negative finding (mean scores: 0.6, 6.0, and 1.6; SDs: 1.1, 4.2, and 2.0) (Table 6). The difference in scores on the positive feelings subscale was statistically significant at the 0.05 level (p value: 0.011) (Table 6). The difference in scores on the uncertainty subscale was borderline significant (p value 0.088) (Table 6). Patients from the three groups had similar scores on the privacy concerns subscale, as well as the physical component of the VR-12, the mental component of the VR-12, the GAD-7, the PHQ-9, and the MHI-5 (Table 6). For construct validity, the uncertainty and privacy concerns subscales were not correlated with established measures for anxiety and depression (Table 7), which supported our hypothesis. The positive feelings and negative emotions subscales were not correlated with established measures (Table 7), which contradicted our hypothesis.

Table 6 Subscale internal consistencies, test-retest reliability, and scores by genomic test findings ($N = 122$)

Scale and range of score FACToR	Alpha ($N = 122$) Coefficient (95% CI)	Test-retest ($n = 26$)[a] Coefficient (95% CI)	Negative ($n = 85$) Mean (SD)	Positive ($n = 12$) Mean (SD)	VUS ($n = 25$) Mean (SD)	P value[b]
Negative emotions, 0–12	0.66 (0.55–0.77)	0.65 (0.24–0.84)	0.6 (1.1)	1.6 (2.7)	0.8 (1.6)	0.202
Positive feelings, 0–16	0.78 (0.71–0.84)	0.83 (0.63–0.92)	6.0 (4.2)	10.0 (2.4)	8.0 (4.3)	0.011
Uncertainty, 0–12	0.72 (0.64–0.8)	0.91 (0.80–0.96)	1.6 (2.0)	3.6 (2.9)	2.3 (2.8)	0.088
Privacy concerns, 0–8	0.70 (0.61–0.79)	0.86 (0.69–0.94)	0.6 (1.4)	0.7 (1.2)	0.6 (1.8)	0.841
VR-12						
Physical component, 0–100	0.93 (0.91–0.95)	NA	45.4 (12.6)	45.4	50.0 (9.6)	0.115
Mental component, 0–100	0.88 (0.85–0.91)	NA	50.3 (9.9)	(13.6) 50.1 (10.0)	49.2 (8.9)	0.621
GAD-7, 0–21	0.89 (0.86–0.92)	NA	3.3 (4.3)	3.0 (4.8)	3.2 (3.2)	0.874
PHQ-9, 0–27	0.86 (0.82–0.89)	NA	4.0 (4.6)	4.8 (6.1)	3.4 (3.0)	0.696
MHI-5, 0–100	0.88 (0.84–0.91)	NA	77.7 (17.4)	73.3 (20.8)	77.0 (14.1)	0.735

[a] Four participants in the test-retest population had missing data and were excluded

[b] P values from one-way ANOVA comparing mean scores of the FACToR subscales and other established instruments among participants receiving negative, positive, and VUS test results

Table 7 Construct validity of the FACToR subscales ($N = 122$)

FACToR subscale	VR-12 mental	GAD-7	PHQ-9	MHI-5
	Pearson's correlation coefficient (P value)			
Negative emotions	− 0.08 (0.345)	0.13 (0.138)	0.04 (0.624)	− 0.07 (0.427)
Positive experience	0.08 (0.388)	− 0.12 (0.170)	− 0.07 (0.461)	0.13 (0.161)
Uncertainty	− 0.04 (0.657)	0.04 (0.679)	− 0.01 (0.925)	− 0.02 (0.799)
Privacy concerns	0.10 (0.268)	− 0.13 (0.144)	− 0.11 (0.220)	0.14 (0.127)

Test-Retest Reliability

All four subscales of the FACToR demonstrated good test-retest reliability: the ICC was 0.65 (95% CI: 0.24–0.84) for the negative emotions subscale, 0.83 (95% CI: 0.63–0.92) for the positive feelings subscale, 0.91 (95% CI: 0.80–0.96) for the uncertainty subscale, and 0.86 (95% CI: 0.69–0.94) for the privacy concern subscale (Table 6).

Discussion

In this study, we developed and conducted preliminary validation of a brief instrument, the FACToR (Table 1 in Online Appendix), which measures the psychosocial impact of receiving genomic findings. Our findings indicate the 12-item FACToR with four subscales is a valid and reliable instrument in a sample of patients who were referred for genomic testing for CRCP. Established instruments that measure general depressive or anxiety symptoms not specific to genomic testing (the VR-12 mental component, the GAD-7, the PHQ-9, and the MHI-5) were not discriminative in this study.

The difference in discriminative ability and the lack of correlation between the FACToR subscales and the other established instruments that measure depression and anxiety in general underline the importance of using an instrument that is sensitive to the psychological consequences specific to genomic testing. The VR-12 mental component, the GAD-7, the PHQ-9, and the MHI-5 were unlikely to capture the uncertainty of the implication of the test result, the ability to plan for the future, or the relief from receiving genomic information. Previous studies have used mostly, among others, the Impact of Event Scale (Weiss & Marmar, 1996), the State-Trait Anxiety Inventory (Spielberger, 1989), and the Hospital Anxiety and Depression Scale (Snaith, 2003) to measure distress, anxiety, and depression following the receipt of genomic test results. The MICRA includes uncertainty as a subscale, along with positive experiences and distress, and asks one question on privacy concern that is related to access to health insurance. The MICRA was developed specifically for cancer and since its development, it has been used mostly in *BRCA1/2* testing and genomic testing for colorectal cancer (Graves et al., 2011, 2012, 2013; Halbert et al., 2011; Lewis et al., 2016; Manchanda et al., 2015; Myers et al., 2011; O'Neill et al., 2009; Rini et al., 2009; Watts et al., 2012; Weinberg et al., 2014; Westin et al., 2011). It was also modified and used in two studies of genomic testing for type 2 diabetes, although neither study reported how it was modified or whether the modified MICRA was validated (Cho et al., 2012; Voils et al., 2012). In the past decade, a few new scales have been developed to assess the psychological impact of genomic testing in other disease areas. The REVEAL Impact of Genetic Testing for Alzheimer's disease (IGT-AD), based on the MICRA, was designed for genetic susceptibility testing for Alzheimer's disease and comprises a distress subscale and a positive subscale (Chung et al., 2009). The Perceptions of Uncertainties in Genome Sequencing (PUGS) was designed to specifically capture the dynamic state of perceived uncertainty associated with genomic test result in various diseases (Biesecker et al., 2017).

The FACToR addresses an important need in the field by including all important dimensions from existing instruments: positive feelings/experiences, negative emotions/distress, uncertainty, and privacy concerns. It was designed specifically for genomic testing, and to be used eventually in other diseases and clinical contexts (e.g., diagnostic, prognostic, etc.). Validation of the FACToR in other disease areas is currently underway at other sites of the CSER consortium, of which this study is a part. The 12-item, self-report questionnaire can be completed in less than 5 min, and thus can be widely used without imposing significant burden on respondents, healthcare providers, or researchers. The four subscales may also be used independently to evaluate distinct components of the testing experience. Some may prefer, for completeness of coverage, to use all 18 items (or all 26 if certain conditions are met) in future assessments; in that context, revalidation is critical. Although in this validation study incidental findings unrelated to CRCP were not returned to the participants and their psychological impacts not captured, its focus on genomic testing makes the FACToR a likely good measure for assessing the psychological impact of receiving incidental findings as well.

This study has several important limitations. First, the FACToR was validated in a sample of racially homogeneous (predominantly white), middle-aged, highly educated, insured patients who were at high risk for CRCP. The baseline mental health functioning of the study participants was within normal limits on most instruments administered in the trial. However,

previous studies have found that women, younger patients, nonwhites, and patients with less formal education and less social support experienced higher levels of depression and/or anxiety following hereditary colorectal cancer testing; patients with higher distress at baseline were more likely to worry about receiving a positive test result and coping with it (Gritz et al., 1999; Vernon et al., 1997). The very resilient sample in this study may explain the floor/ceiling effect of some items of the FACToR and the similar levels of depression and anxiety measured by established depression and anxiety scales among patients receiving different types of genomic test results. Second, the small sample size of this study limited our ability to stratify this analysis based on cancer status. Evidence suggested that patients without a personal history of cancer experienced increased distress from genomic test results during the immediate post-disclosure time period while those with a personal history of cancer had stable psychological outcomes over time that were within normal limits (Ellen R. Gritz et al., 2005). In our study sample, approximately one third of the participants had been previously diagnosed with colorectal cancer, and their responses to a positive or a VUS genomic test result may differ from those who were had not been diagnosed with colorectal cancer. Third, because of the small sample sizes of the subgroups (those who have discussed genetic test results with family, those who have children, and those who currently have cancer or have had it in the past), items 19–26 were not included in this validation. However, these items are relevant and should be included in future validation studies when the sample size is large enough. Fourth, in this study, focus groups and cognitive interviews were conducted with patients with hereditary CRCP predisposition, which limited the FACToR's content validity in other disease areas. Further development and validation of the instrument in other disease areas is currently underway at other sites of the CSER 2 consortium (*https://cser-consortium.org*). Fifth, the negative emotions subscale included an item that has a low factor loading (0.36), an item that demonstrated floor/ceiling effect, had the lowest alpha among all four subscales (0.66), and did not demonstrate known-group validity. As a result, scores on this subscale should be interpreted with caution and more qualitative and quantitative assessments of this subscale with a larger sample size in a more diverse population are needed. Sixth, although some of the FACToR subscale scores have demonstrated known-group validity, the clinical significance of elevated scores remains to be evaluated. Last but not least, although the FACToR was administered regularly in the NEXT Medicine Study, the FACToR's responsiveness to change was not assessed in this analysis.

In conclusion, we developed a new instrument, the FACToR, which can help assess psychological responses of patients who undergo genomic testing, and we validated it in a high-risk colorectal cancer setting. This is the critical first step toward developing and validating an instrument that can be used in multiple settings and for multiple conditions. Efforts are currently underway to validate the FACToR in other disease areas. As genomic testing is moving quickly into clinical research and practice, the FACToR fills an important gap by providing a measurement of the psychological impact of genomic testing, a critical component of assessing the risks and benefits of such technologies. Future studies should evaluate the reliability and validity of the FACToR in more sociodemographically diverse populations as well as in other diseases and risk groups, with larger sample sizes that would allow stratified analyses based on disease status. Additional research should also examine the FACToR's responsiveness to change over time and evaluate potential effect sizes to enhance the interpretability of the scale.

Author Contributions Section Meng Li, Caroline S. Bennette, David L. Veenstra and Donald L. Patrick contributed to the design of the work, analysis and interpretation of data, and drafting and revising the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Laura M. Amendola, M. Ragan Hart, Patrick Heagerty, Bryan Comstock, Peter Tarczy-Hornoch, Stephanie M. Fullerton, Dean A Regier, Wylie Burke, Susan B. Trinidad and Gail P. Jarvik contributed to the acquisition of data and critical revisions of the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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Compliance with Ethical Standards

Conflict of Interest Authors Meng Li, Caroline S. Bennette, Laura M. Amendola, M. Ragan Hart, Patrick Heagerty, Bryan Comstock, Peter Tarczy-Hornoch, Stephanie M. Fullerton, Dean A Regier, Wylie Burke, Susan B. Trinidad, Gail P. Jarvik, David L. Veenstra, and Donald L. Patrick declare that they have no conflict of interest.

Informed Consent This study obtained informed consent from all study participants.

Human Studies and Informed Consent This study was approved by the University of Washington Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Animal Studies No animal studies were carried out by the authors for this article.

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