PEC Innovation 2 (2023) 100124

Contents lists available at ScienceDirect

PEC Innovation

journal homepage: www.elsevier.com/locate/pecinn

Development of a novel measure of advanced cancer patients' perceived utility of secondary germline findings from tumor genomic profiling

Jada G. Hamilton [a,b,c,*], Ibrahim H. Shah [a], Caroline Salafia [a,d], Elizabeth Schofield [a], Margaux Genoff Garzon [a], Kechna Cadet [a], Zsofia K. Stadler [b,e], Jennifer L. Hay [a,c], Kenneth Offit [b,e], Mark E. Robson [b,e]

[a] Department of Psychiatry & Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[b] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[c] Department of Psychiatry, Weill Cornell Medical College, Cornell University, New York, NY, USA
[d] Department of Human Development and Family Sciences, University of Connecticut, Storrs, CT, USA
[e] Department of Medicine, Weill Cornell Medical College, Cornell University, New York, NY, USA

ARTICLE INFO

Keywords:
Genomic sequencing
Genetic testing
Secondary germline findings
Incidental germline findings
Oncology
Perceived utility
Tumor-normal analysis

ABSTRACT

Objective: Tumor genomic profiling (TGP) can inform advanced cancer patients' treatment decisions, and also reveal secondary germline findings—information about inherited risks for cancer and other disorders. We sought to develop a measure of patient perceptions of the clinical and personal utility of secondary germline findings.
Methods: We developed a draft survey based on literature and patient interview data ($n = 40$). We evaluated and refined the survey through cognitive interviews with advanced cancer patients who received secondary germline findings from TGP ($n = 10$). The survey was psychometrically validated with data from two independent samples of advanced cancer patients undergoing TGP (total $n = 349$).
Results: Cognitive interviews offered opportunities for survey refinement and confirmation of its comprehensible nature. Exploratory and confirmatory factor analysis of the survey identified 16 items across three subscales with strong internal consistency (Cronbach's alpha ≥ 0.79): perceived utility for others, perceived utility for self and health, and confidence in secondary findings.
Conclusion: We developed a novel valid scale with promise for measuring advanced cancer patients' perceptions of the utility of secondary germline findings.
Innovation: We offer a new patient-derived measure of perceived utility of and confidence in secondary germline findings with potential applications for precision oncology research and clinical communication.

1. Introduction

Genome sequencing technology is being used as part of precision oncology to evaluate the tumors of cancer patients to identify genetic variants that suggest susceptibility to approved or experimental targeted therapeutics. Through such "tumor genomic profiling" (TGP), germline variants indicative of inherited disease risks may be identified (detected either within tumor DNA or when a patient's germline DNA is directly sequenced for comparison to the tumor sequence). These germline findings are considered "secondary" when actively sought (or "incidental" when not) because they arise outside of the original purpose of TGP [1,2]. Secondary germline findings may indicate inherited risks for various health conditions with important implications for patients and their families, and are likely to be detected in a sizable minority of cancer patients (e.g., 15.7%) [3].

A high level of interest appears to exist among cancer patients regarding the receipt of secondary germline findings from TGP [4-11]. Less clear, however, are patients' perspectives regarding the overall value or utility of secondary germline findings. Traditionally, experts have defined the value of genetic risk information as a function of its clinical utility, or its ability to improve morbidity and mortality by influencing medical decisions or management [12,13]. Indeed, clinical utility is a guiding principle for expert recommendations about the return of secondary germline variants arising from clinical sequencing, including current recommendations from the American College of Medical Genetics and Genomics (ACMG) to allow patients to opt-out of receiving secondary findings regarding pathogenic/likely pathogenic variants in 73 medically actionable genes [14-18]. Qualitative work indicates that many cancer patients expect such health benefits to be derived from the

Abbreviations: ACMG, American College of Medical Genetics and Genomics; ASCO, American Society of Clinical Oncology; CFA, Confirmatory factor analysis; EFA, Exploratory factor analysis; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; TGP, Tumor genomic profiling.

* Corresponding author at: Memorial Sloan Kettering Cancer Center, 633 3rd Avenue, 4th floor, New York, NY 10017, USA.
E-mail address: hamiltoj@mskcc.org (J.G. Hamilton).

http://dx.doi.org/10.1016/j.pecinn.2023.100124
Received 14 October 2022; Received in revised form 6 January 2023; Accepted 17 January 2023
Available online xxxx

receipt of secondary germline findings for themselves or for their families [5,8,19,20].

It has also been argued that genetic information can have personal utility (i.e., benefits beyond a reduction in one's morbidity or mortality) [13,21-23]. Such aspects of personal utility have been posited to span various domains, including affective/emotional (e.g., improving coping, mental preparation), cognitive (e.g., self-knowledge, curiosity), behavioral (e.g., future planning including reproduction, family communication), and social (e.g., research altruism, stigma and discrimination) outcomes [24-26]. How individuals construct and perceive such personal utility may vary based on the clinical context and their role in that context [21,23,27]. Studies of cancer patients' attitudes regarding genomic sequencing suggest that dimensions of personal utility, such as being able to make more informed decisions about the future, resolve feelings of curiosity, maintain hope, and make a contribution to medical research, could arise from learning secondary germline findings [5,8,28-30]. Further, as argued by Bunnik and colleagues [23], personal utility "presupposes two things: that a genomic test delivers *information* (i.e., meaningful information) and that this information can be *used* or *put to use* in some reasonable way (page 324)." Thus, the perceived interpretability, quality, and actionability of the genetic information provided may be important contributors to the utility derived therein by patients.

Acquiring an understanding of patients' expectations and perceptions regarding the utility of secondary germline findings is important because these beliefs represent health cognitions that may influence their decisions to receive such information [31-33], as well as their psychological reactions, information processing, communication, and health behaviors following receipt of these results [34-36]. However, to our knowledge no validated measures currently exist for measuring these beliefs among cancer patients undergoing TGP. To date, TGP has largely been limited to cancer patients with advanced disease to identify eligibility for clinical trials of novel therapeutics [37,38]. An individual's perspective about utility is context- and role-specific [21,23,27], and patients with advanced cancer have distinct experiences and challenges that likely shape the domains of clinical and personal utility that are most relevant to their evaluation of secondary germline findings from TGP. For instance, patients with advanced cancer have fewer opportunities to derive behavioral utility associated with future reproductive choices given their generally poor prognosis and are less likely to encounter social utility outcomes involving personal insurance or employment discrimination given their existing cancer diagnoses than other populations who have been the focus of investigations of the utility of genetic risk information (e.g., healthy adults undergoing genomic sequencing [25,39], parents/caregivers of pediatric cancer patients or those seeking to resolve a diagnostic odyssey [27]). Yet, patients with advanced cancer may have a heightened focus on the clinical utility of secondary germline findings for the immediate medical management of their existing cancer, and the cognitive insights to be gained by family members who are more likely to derive preventive benefits from the information. With the present study, we adopted a multiphase approach to develop and evaluate the initial psychometric properties of a new measure of advanced cancer patients' perceptions of the clinical and personal utility of secondary germline findings arising from TGP. Our measure development was consistent with existing conceptual models of patient perceptions of clinical and personal utility of genetic risk information [24,26,27], yet was intended to reflect outcomes most relevant to the advanced cancer patient population in the clinical context of TGP. We also incorporated outcomes related to a patient's interpretability, quality, and actionability of the genetic risk information in this measure development, given that such dimensions may theoretically serve as a necessary precondition to the perceived utility of secondary germline findings [23].

2. Methods

We followed Rothrock and colleagues' [40] recommendations for developing a patient-reported outcome measure (see Fig. 1). Phase 1 of this approach centered upon gathering input to inform the creation of potential survey items for measuring the construct of perceived utility of secondary germline findings arising from TGP. Phase 2 involved using qualitative cognitive interviews to refine and improve the items. Phase 3 involved the preliminary psychometric validation of the resulting survey measure in two samples of cancer patients receiving secondary germline findings from TGP. This research was approved by the Memorial Sloan Kettering Cancer Center Institutional Review Board.

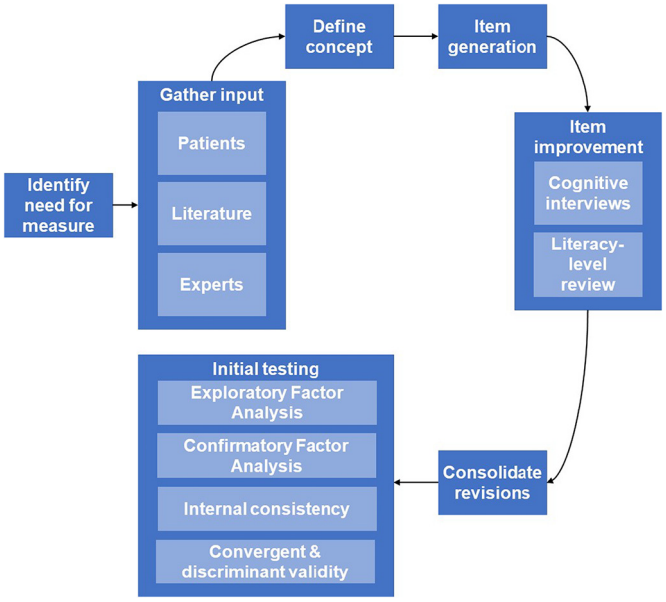

Fig. 1. Approach to developing a new measure of cancer patients' perceived utility of secondary germline findings from tumor genomic profiling. This multi-phase approach to patient-reported outcome measure development is adapted from that of [40].

2.1. Phase 1: item generation

Our multidisciplinary team of experts in social and health psychology, clinical psychology, clinical genetics, and qualitative methodology generated survey items through a combination of literature review and patient input. Relevant theoretical and empirical literature regarding clinical and personal utility of genomic sequencing and patient perceptions and expectations of genetic/genomic testing were reviewed to identify possible domains and items. Several items from existing measures of the perceived value of genomic sequencing results [41] and motivations about genetic testing for hereditary cancer syndromes [42] were adapted to be relevant to the context of secondary germline findings among advanced cancer patients. Additionally, we reviewed previously-collected qualitative data from advanced cancer patients regarding their attitudes about the possible receipt of secondary germline findings from TGP. Details of this study are reported elsewhere [8], but in brief, in-depth interviews were conducted with 40 patients diagnosed with breast, colorectal, lung, or bladder cancer (63% female, ages 30-82 years, 85% white, 95% non-Hispanic, 56% college graduates). All participants had undergone TGP with the MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets) test [43,44], a sequencing panel that at that time detected somatic variants in 410 cancer-related genes with analysis of a matched normal sample and germline subtraction, and interviews focused on the hypothetical decision of learning secondary germline findings. These data indicated various perceived benefits and expectations regarding the potential uses of secondary germline findings, which informed item generation. Through these sources, we created a draft survey consisting of 19 items rated on a Likert-type scale from 1 = "strongly disagree" to 5 = "strongly agree" (Table 1). We selected a 5-point Likert-type scale to allow for a neutral point, to minimize participant burden (e.g., versus a 7- or 9- point

Table 1
Development of survey items to assess cancer patients' perceived utility of secondary germline findings from tumor genomic profiling.

Original Item Wording	Participant Cognitive Interview Feedback	Final Item Wording (for use prior to receiving secondary germline findings, e.g., Sample 1)	Final Item Wording (for use after receiving secondary germline findings, e.g., Sample 2)
1. My secondary findings can help reduce my family's chances of getting cancer.	None	1. My secondary findings will help reduce my family's chances of getting cancer.	1. My secondary findings will help reduce my family's chances of getting cancer.
2. My secondary findings will be valuable for maintaining my future health.	Round 1 interviews suggested replacing "valuable" with "helpful."	2. My secondary findings will be helpful for maintaining my future health.	2. My secondary findings are helpful for maintaining my future health.
3. My secondary findings can be useful to my doctor.	None	3. My secondary findings will be useful to my doctor.	3. My secondary findings are useful to my doctor.
4. My secondary findings can be useful to my family.	None	4. My secondary findings will be useful to my family.	4. My secondary findings are useful to my family.
5. I trust that my secondary findings will be accurate.	None	5. I trust that my secondary findings will be accurate.	5. I trust that my secondary findings are accurate.
6. I am confident that I understand my secondary findings.	Round 2 interviews suggested minor confusion due to the complex nature of the test results themselves.	6. I am confident that I will be able to understand my secondary findings.	6. I am confident that I am able to understand my secondary findings.
7. I would recommend tumor genomic profiling to a close friend or family member who had cancer.	None	7. I would recommend tumor genomic profiling to a close friend or family member who had cancer.	7. I would recommend tumor genomic profiling to a close friend or family member who had cancer.
8. My secondary findings are easy to understand.	None	8. My secondary findings will be easy to understand.	8. My secondary findings are easy to understand.
9. My secondary findings make me feel less confused about my cancer.	None	9. My secondary findings will make me feel less confused about my cancer.	9. My secondary findings make me feel less confused about my cancer.
10. My decisions about managing my health are easier to make because of my secondary findings.	None	10. My decisions about managing my health will be easier to make because of my secondary findings.	10. My decisions about managing my health are easier to make because of my secondary findings.
11. My secondary findings can help me understand my health better.	Round 1 interviews suggested replacing "better" with "in general."	11. My secondary findings will help me understand my health in general.	11. My secondary findings help me understand my health in general.
12. My secondary findings can help me to plan for my future.	None	12. My secondary findings will help me to plan for my future.	12. My secondary findings help me to plan for my future.
13. My doctor can understand my secondary findings.	Omitted based on Round 2 interviews.		
14. The meaning of my secondary findings could change as scientists learn more about genes and diseases.	None	13. The meaning of my secondary findings could change as scientists learn more about genes and diseases.	13. The meaning of my secondary findings could change as scientists learn more about genes and diseases.
15. I am in a better position to make decisions about my health now that I know my secondary findings.	None	14. I will be in a better position to make decisions about my health when I know my secondary findings.	14. I am in a better position to make decisions about my health because I know my secondary findings.
16. My secondary findings can help doctors learn to care for future patients.	None	15. My secondary findings can help doctors learn to care for future patients.	15. My secondary findings can help doctors learn to care for future patients.
17. My tumor genomic profiling can help my doctor treat my cancer.	None	16. My tumor genomic profiling can help my doctor treat my cancer.	16. My tumor genomic profiling can help my doctor treat my cancer.
18. I am confident that if I want to share my secondary findings with other people, I can do so.	None	17. I am confident that if I want to share my secondary findings with other people, I can do so.	17. I am confident that if I want to share my secondary findings with other people, I can do so.
19. The information that I learn from my secondary findings is valuable.	Omitted based on Round 1 interviews.		

Note: The above items are preceded by the following introduction: "'Secondary findings' is a term that we use to describe the genetic changes in the genes of your normal cells that could be found with tumor genomic profiling. On the one hand, tumor genomic profiling could show that you have one or more genetic changes in your normal cells that increase your risk for getting a disease. On the other hand, tumor genomic profiling could show that you do not have any genetic changes in your normal cells that increase your risk for getting a disease. Both of these kinds of results are 'secondary findings.' Please indicate how strongly you agree with each of the following statements with regards to your expectations about the secondary findings that you (will receive/have received) from tumor genomic profiling." All items use a 5-point Likert-type response scale (1 = strongly disagree, 2 = somewhat disagree, 3 = neither disagree nor agree, 4 = somewhat agree, 5 = strongly agree).

scale), and because we did not anticipate that the nuance of patients' perceptions would necessitate additional response options.

2.2. Phase 2: item improvement

Two rounds of cognitive interviews were conducted with patients (n = 5/round) to refine the survey, consistent with recommended methods [45] and guidance that seven to ten interviews are generally sufficient to achieve patient consensus about the form and structure of a measure [46]. Cognitive interviewing is an FDA-recommended, gold-standard method for developing and adapting patient-facing materials [45,47]. Eligible patients included those who were age 18 or older, lived in the New York metro-area, spoke English, were diagnosed with a solid tumor, and had previously received secondary germline findings (either a pathogenic/likely pathogenic variant or confirmation of no pathogenic/likely pathogenic variants) from TGP with the MSK-IMPACT test. Participants were recruited by telephone, provided verbal informed consent, and mailed a copy of the draft survey. Interviews were conducted by one of two trained team members by telephone. Participants reviewed the survey and were asked to "think aloud" as they answered each item. Interviewers used a series of standard probes to elicit participants' perceptions and understanding of specific items and the whole survey. Participants were encouraged to express their ideas about additional aspects of the clinical and personal utility of secondary germline findings based on their direct experiences. Interviews were audio-recorded and lasted approximately 30 minutes; participants received $20 in appreciation of their contributions.

Four members of the study team analyzed interview transcripts through a process of thematic content analysis to identify converging instances of participant problems, difficulties, or suggestions regarding the survey [45,48-51]. Following the first round of interviews, analysis of these data determined whether any interim revisions were warranted based on participant feedback. Content endorsed by at least two participants as being problematic was revised for testing in the second round of cognitive interviewing. An identical procedure was used for the second round of

interviews to further refine the survey. Upon completion of this process, the literacy level of the survey was determined using the Flesch-Kincaid grade score, a measure of readability that indicates the US school grade level at which a reader can understand at least 50% of the content [52]. The American Medical Association recommends that health-related materials be written at the 5th-6th grade level [53], and the National Institutes of Health recommend that materials be written at the 3rd-5th grade level to ensure comprehension by those of lower literacy levels [54].

2.3. Phase 3: psychometric validation

Psychometric validation data were drawn from two independent samples. Sample 1 (longitudinal sample; $n = 226$) consisted of data collected in an ongoing, prospective study of cancer patients' experiences with TGP and secondary germline findings. Analyzed data were collected at study baseline, a timepoint following patient consent to both TGP with the MSK-IMPACT test and to receive any identified pathogenic/likely pathogenic secondary germline findings in ≥76 cancer predisposition genes, but before receipt of these results. Participants completed a self-report questionnaire that included the 17-item perceived utility survey, plus measures of demographic (including health status assessed with the ECOG Performance Status [55] and self-reported health assessed with an item from the NCI-sponsored Health Information National Trends Survey [56]), cognitive (including knowledge about TGP and secondary germline findings assessed with an investigator-designed scale, satisfaction with the educational video used to facilitate TGP consent assessed with an investigator-designed item, satisfaction with information provided in the consent process assessed with an investigator-designed item, decisional conflict about learning secondary germline findings assessed with the validated Decisional Conflict Scale [57], and perceived risk of receiving a pathogenic/likely pathogenic secondary germline finding assessed with a modified item from the NCI-sponsored Health Information National Trends Survey [56]), and emotional (including anxiety and depression assessed by the Hospital Anxiety and Depression Scale [58]) variables. Sample 2 (cross-sectional sample; $n = 123$) consisted of data from a retrospective cross-sectional questionnaire of cancer patients who had undergone the MSK-IMPACT test and had received a pathogenic/likely pathogenic secondary germline finding in any of ≥76 cancer predisposition genes. Participants completed a self-report questionnaire online that included the 17-item perceived utility survey and measures of demographic (including above measures of health status and self-reported health), cognitive (including above measure of satisfaction with information, as well as dissatisfaction with healthcare provider support following receipt of secondary germline findings assessed with an investigator-designed item, and communication self-efficacy for sharing one's secondary germline findings with others assessed with an investigator-designed scale modeled after [59]), and emotional (including genetic testing concerns assessed with the total score from an adapted version of the Multidimensional Impact of Cancer Risk Assessment [60]) variables.

We used exploratory factor analysis (EFA) to examine the underlying structure of the perceived utility measure in Sample 1—the larger available sample and that which we anticipated would have greatest variability in responses given that the timing of data collection meant that these participants were reporting on their anticipated utility of the secondary germline findings. We then used confirmatory factor analysis (CFA) in Sample 2. Prior to factor analysis, the two samples were described and compared on demographic, disease, cognitive, and emotional variables using t-tests and Chi-square tests. For the EFA, we used maximum likelihood as the extraction method with a Promax oblique rotation allowing for intercorrelation of factors. We assessed eigenvalues and followed a cutoff value of 1.0. In the event of an item cross-loading across factors, factor assignment was based on the highest factor loading and consideration of the item's conceptual fit with other items within the factor. Items were considered for deletion based on their conceptual fit with other items within the factor and whether their removal improved the internal consistency of the factor. For the CFA, we assessed RMSEA, CFI, and TLI for overall fit, and compared these to a single factor model using AIC and BIC [61]. Internal consistency was assessed for both samples using Cronbach's alpha.

Next, the samples were combined, and factor scores calculated for each participant as an average of the constituent items. Convergent and discriminant validity was assessed by correlation of the factor scores with demographic, disease, cognitive, and emotional variables that were collected in each sample. Consistent with theoretical models of health decision-making (e.g., the Ottawa Decision Support Framework, [31-33]), we posited that perceived utility about secondary germline findings is a health cognition that would be positively related to one's knowledge about these results and inversely related to one's uncertainty. Thus, we predicted a priori that heightened perceived utility would be associated with greater knowledge, satisfaction with the educational video, and satisfaction with information, and associated with lower decisional conflict about learning secondary germline findings. Given the context-specific characteristics of the advanced cancer patient participants, we also predicted that those with lower health status may hold particularly optimistic beliefs about the utility of secondary germline findings, and that the preventive value of these results to family would lead to a positive association of these beliefs with communication self-efficacy. We further anticipated no correlation of these health cognitions with the assessed emotional outcomes. All analyses were conducted using SAS version 9.4. Type I error rate for correlations was set to $\alpha = 0.05$.

3. Results

3.1. Phase 2: item improvement

Cognitive interviews were conducted with 10 total participants (70% female, ages 53-76, 40% with pathogenic/likely pathogenic secondary findings). In the first round of interviews, two items were noted as being difficult to comprehend and thus candidates for revision. The first item ("My secondary findings will be valuable for maintaining my future health") implied an association with money or financial value to several participants. The second item ("My secondary findings can help me understand my health better") was interpreted as being specific to cancer rather than overall health by a few participants. Participant suggestions were used to rephrase these items for testing in the second round of cognitive interviews (see Table 1). Another item ("The information that I learn from my secondary findings is valuable") was perceived as redundant by a few participants and was subsequently omitted. In the second round of cognitive interviews, the two rephrased items performed well, prompting no concerns or questions among participants. An additional item ("My doctor can understand my secondary findings") was considered problematic and confusing to many participants and was removed from the final survey. One item ("I am confident that I understand my secondary findings") was noted as somewhat ambiguous by a participant because of the inherently complex nature of secondary germline findings and was reworded slightly in the final version of the survey to assess one's general ability to understand the results.

Overall, participants in both rounds of cognitive interviews found the survey to be clear, easy to understand, and acceptable in length. The majority indicated that it was easy to answer the survey questions and did not experience difficulties with the response scale (Fig. 2). The final survey consisted of 17 items and retained the 5-point Likert-type response scale. As shown in Table 1, item wordings (e.g., verb tenses) were modified slightly to create versions to assess perceived utility either prior to or after the receipt of secondary germline findings. Analysis of the literacy level of both versions of the final survey (including the introductory language defining the term "secondary findings") indicated a Flesch-Kincaid grade level of 8.6-8.8. Given the sensitivity of the Flesch-Kincaid grade level to multisyllabic words, we also calculated the literacy level when replacing "secondary findings" in each item with the synonym "results" and "tumor genomic profiling" with "test." This scenario produced a Flesch-Kincaid grade level of 6.2-6.3.

3.2. Phase 3: psychometric validation

As shown in Table 2, the two samples were fairly homogenous in participant age, race, education, and income. Most participants were in their 50s

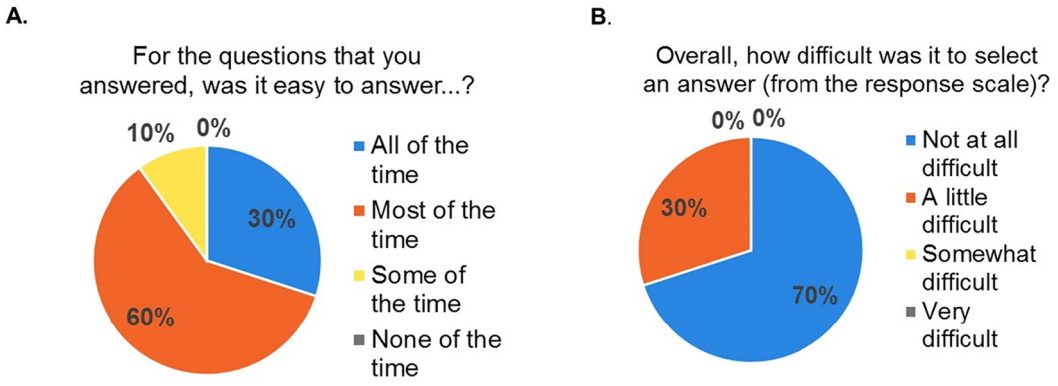

Fig. 2. Cognitive interview participant feedback ($n = 10$) regarding: (A) the ease of answering survey items and (B) the difficulty of using the item response scale.

Table 2
Characteristics of samples used for psychometric validation.

Variable	Range	Sample 1 $n = 226$ *M (SD)*	Sample 2 $n = 123$ *M (SD)*	All $N = 349$ *M (SD)*	*p*
Female, *n* (%)	NA	129 (57%)	52 (42%)	181 (52%)	0.008
Age (years)	20 – 89	58.5 (13.2)	61.7 (12.6)	59.6 (13.0)	0.026
Race, *n* (%)	NA				<0.001
American Indian or Alaskan		0 (0%)	1 (1%)	1 (0%)	
Asian		7 (3%)	1 (1%)	8 (2%)	
Black		20 (9%)	1 (1%)	21 (6%)	
White		185 (82%)	109 (89%)	294 (84%)	
Other		5 (2%)	0 (0%)	5 (1%)	
Missing		9 (4%)	11 (9%)	20 (6%)	
Hispanic, *n* (%)	NA	16 (8%)	4 (4%)	20 (6%)	0.153
Annual Household Income, *n* (%)	NA				0.003
$10k – <$35k		12 (5%)	3 (2%)	15 (4%)	
$35k – <$50k		10 (4%)	5 (4%)	15 (4%)	
$50k – <$75k		18 (8%)	5 (4%)	23 (7%)	
$75k – <$100k		32 (14%)	4 (3%)	36 (10%)	
$100k – <$200k		60 (27%)	33 (27%)	93 (27%)	
$200k or more		47 (21%)	40 (33%)	87 (25%)	
Missing		47 (21%)	33 (27%)	80 (23%)	
Education, *n* (%)	NA				<0.001
8 – 11 years		4 (2%)	0 (0%)	4 (1%)	
Completed high school		17 (8%)	5 (4%)	22 (6%)	
Post-secondary training		10 (4%)	0 (0%)	10 (3%)	
Some college		28 (12%)	10 (8%)	38 (11%)	
College graduate		85 (38%)	35 (28%)	120 (34%)	
Postgraduate		71 (31%)	63 (51%)	134 (38%)	
Missing		11 (5%)	10 (8%)	21 (6%)	
Metastatic Disease, *n* (%)	NA	160 (71%)	102 (83%)	262 (75%)	0.017
Cancer Diagnosis, *n* (%)	NA				NA
Bladder		10 (4%)	9 (7%)	19 (5%)	
Breast		42 (19%)	11 (9%)	53 (15%)	
Colorectal		41 (18%)	14 (11%)	55 (16%)	
Pancreatic		24 (11%)	8 (7%)	32 (9%)	
Prostate		29 (13%)	36 (29%)	65 (19%)	
Other gastrointestinal		32 (14%)	8 (7%)	40 (12%)	
Other reproductive		28 (12%)	19 (15%)	47 (13%)	
Other solid tumor (including melanoma)		20 (9%)	18 (15%)	38 (11%)	
Time since receiving secondary germline findings (months)[2]	1 – 58	NA	16.9 (9.3)	16.9 (9.3)	NA
ECOG	2 – 5	4.4 (0.7)	4.6 (0.7)	4.5 (0.7)	0.011
Self-reported Health	1 – 5	3.3 (1.1)	3.4 (1.0)	3.4 (1.1)	0.605
Knowledge[1]	0 – 100	56.9 (21.2)	NA	56.9 (21.2)	NA
Satisfaction with Educational Video[1]	1 – 5	3.9 (1.1)	NA	3.9 (1.1)	NA
Satisfaction with Information	1 – 5	4.4 (0.9)	4.4 (1.0)	4.4 (0.9)	0.673
Dissatisfaction with Healthcare Provider Support[2]	1 – 5	NA	1.9 (1.2)	1.9 (1.2)	NA
Decisional Conflict[1]	0 – 100	24.5 (19.0)	NA	24.5 (19.0)	NA
Perceived Risk[1]	1 – 5	3.5 (0.9)	NA	3.5 (0.9)	NA
Communication Self-Efficacy[2]	7 – 28	NA	19.6 (6.3)	19.6 (6.3)	NA
Anxiety[1]	0 – 19	6.3 (4.5)	NA	6.3 (4.5)	NA
Depression[1]	0 – 16	4.2 (3.8)	NA	4.2 (3.8)	NA
Genetic Testing Concerns[2]	3 – 72	NA	26.8 (13.4)	26.8 (13.4)	NA

[1] = Measure only captured in longitudinal study with Sample 1.
[2] = Measure only captured in cross-sectional study with Sample 2.

Table 3
Exploratory factor analysis in Sample 1 of survey items to assess cancer patients' perceived utility of secondary germline findings from tumor genomic profiling.

	Factor 1: Perceived utility for others	Factor 2: Perceived utility for self and health	Factor 3: Confidence in secondary findings
1. My secondary findings will help reduce my family's chances of getting cancer.[a]	0.117	0.530	0.062
2. My secondary findings will be helpful for maintaining my future health.	0.534	0.595	-0.041
3. My secondary findings will be useful to my doctor.	0.749	0.358	0.084
4. My secondary findings will be useful to my family.	0.672	0.316	0.237
5. I trust that my secondary findings will be accurate.	0.441	0.292	0.502
6. I am confident that I will be able to understand my secondary findings.	0.426	0.229	0.710
7. I would recommend tumor genomic profiling to a close friend or family member who had cancer.	0.615	0.181	0.484
8. My secondary findings will be easy to understand.	0.119	0.290	0.800
9. My secondary findings will make me feel less confused about my cancer.	0.073	0.675	0.491
10. My decisions about managing my health will be easier to make because of my secondary findings.	0.305	0.767	0.309
11. My secondary findings will help me understand my health in general.	0.286	0.703	0.359
12. My secondary findings will help me to plan for my future.	0.361	0.745	0.223
13. The meaning of my secondary findings could change as scientists learn more about genes and diseases.	0.706	0.221	0.286
14. I will be in a better position to make decisions about my health when I know my secondary findings.	0.456	0.642	0.328
15. My secondary findings can help doctors learn to care for future patients.	0.770	0.203	0.282
16. My tumor genomic profiling can help my doctor treat my cancer.	0.667	0.309	0.050
17. I am confident that if I want to share my secondary findings with other people, I can do so.	0.699	0.086	0.484

Note: Shading indicates the factor to which each item was assigned based on the factor loadings.
[a] Item deleted from the scale based on a lack of conceptual fit with Factor 2 and improved internal consistency of the factor following item removal.

or 60s (median age = 62, IQR = 51–69), and most (84%) reported their race as White. Most (77%) of those reporting education had at least a college degree, with 41% having a postgraduate degree. Two-thirds of those reporting income (67%) reported annual household incomes over $100,000. Three-quarters (75%) of participants had metastatic disease, though the average ECOG score was high with a mean of 4.5 (a value between 4 = "restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature" and 5 = "fully active, able to carry on all pre-disease performance without restriction"). The longitudinal Sample 1 had a greater proportion of females (57% vs. 42%, $p = 0.008$), more participants of color (15% vs. 3%, $p < 0.001$), and lower income (26% vs. 44% over $200,000, $p = 0.003$) compared to the cross-sectional Sample 2. Age, education, ECOG scores, and metastatic disease status also differed slightly, but significantly.

The EFA using the longitudinal Sample 1 suggested three factors. Eigenvalues for the first three factors were 8.77, 1.34, and 1.04, with the fourth eigenvalue (0.88) being well below the cutoff of 1.0. Factor loadings for each of the 17 items across the three factors appear in Table 3. The first factor was identified by the team as encompassing *perceived utility for others* (7 items; e.g., "My secondary findings will be useful to my family"; Cronbach's alpha = 0.90). The second factor was identified as *perceived utility for self and health* (7 items; e.g., "My secondary findings will be helpful for maintaining my future health"); however, one item (item 1: "My secondary findings will help reduce my family's chances of getting cancer") did not fit conceptually with this factor and its removal improved the internal consistency of the factor (Cronbach's alpha change from 0.89 to 0.91). Thus, this item was deleted from the scale for subsequent analyses. The third factor was identified as *confidence in secondary findings* (3 items; e.g., "I am confident that I will be able to understand my secondary findings"; Cronbach's alpha = 0.79). Inter-correlations between the factors ranged between 0.67 and 0.72.

Fit statistics for the CFA in the cross-sectional Sample 2, and also fit statistics for a unidimensional alternative structure, were evaluated and compared (Table 4). The 3-factor solution outperformed the unidimensional solution on RMSEA, AIC, BIC, CFI, and TLI. The CFI was in the acceptable range (0.82); however, the RMSEA (0.14) was slightly above the 0.1 threshold, as was TLI (0.78) slightly below the 0.8 threshold. Cronbach's alphas in this sample were good: 0.84, 0.93, and 0.77, respectively. Overall, perceived utility for others had the highest mean score ($M = 4.3$, $SD = 0.7$), followed by confidence in secondary findings ($M = 4.0$, $SD = 0.7$), and then perceived utility for health and self ($M = 3.7$, $SD = 0.9$). Sample 2 had significantly higher confidence in secondary findings than did Sample 1 ($M_2 = 4.3$, $SD_2 = 0.7$ vs $M_1 = 3.9$, $SD_1 = 0.7$; $p < 0.001$). Sample 2 also had significantly lower perceived utility for health and self than did Sample 1 ($M_2 = 3.5$, $SD_2 = 1.0$ vs $M_1 = 3.8$, $SD_1 = 0.8$; $p = 0.039$). The samples did not differ on perceived utility for others.

Correlations for convergent and discriminant validity appear in Table 5. As predicted, all three factors correlated most strongly to satisfaction with the educational video ($r = 0.45, 0.51, 0.46$, respectively; all $p < 0.001$) and satisfaction with information ($r = 0.40, 0.42, 0.51$, respectively; all $p < 0.001$). The perceived utility for others ($r = 0.24$; $p = 0.011$) and confidence in secondary findings ($r = 0.37$; $p < 0.001$) factors also significantly correlated to communication self-efficacy, such that greater self-efficacy was associated with greater perceived utility for others[1] and confidence. Contrary to predictions, the perceived utility for health and self factor was not associated with communication self-efficacy. Additionally, none of the factors were associated with health status, decisional conflict, or knowledge. While no a prior predictions were made for associations with

[1] It should be noted that the perceived utility for others factor (Factor 1) included one item (item 17: "I am confident that if I want to share my secondary findings with other people, I can do so") that was designed by the study team to assess the patient's perceived interpretability and actionability of information revealed by the secondary germline findings (because preventive health benefits for family can only be accrued if communicated by the patient). However, this item could be interpreted as analogous with the construct of communication self-efficacy. We thus evaluated whether the observed correlation between communication self-efficacy and Factor 1 remained when item 17 was omitted from the factor – in this case, the correlation did not appreciably decrease ($r = 0.20$) and the significance was unchanged. We also evaluated the fit of the overall model when item 17 was omitted from the measure, and observed that Cronbach's alpha for Factor 1 decreased (alpha = 0.88) and the overall model provided a poorer fit to the data. Thus, we elected to retain item 17 within the measure as reported.

Table 4
Confirmatory factor analysis of the 16-item measure in Sample 2 to compare the observed 3-factor model to a unidimensional alternative model.

Fit Indices	3-Factor Model	1-Factor Model
RMSEA	0.144	0.167
CFI	0.816	0.721
TLI	0.782	0.682
AIC	412.0	568.5
BIC	508.4	662.1

Table 5
Correlations between factors and other study variables to evaluate convergent and discriminant validity

Variable	Factor 1: Perceived utility for others	Factor 2: Perceived utility for self and health	Factor 3: Confidence in secondary findings
Gender[a]	0.43	0.66	1.87†
Age	0.04	0.06	**0.12***
Annual Household Income	0.05	0.02	**0.16****
Education	–0.09†	**–0.15****	0.01
Metastatic Disease[a]	0.18	1.08	1.25
ECOG	–0.06	–0.04	0.03
Self-reported Health	0.00	0.01	0.03
Knowledge[1]	0.13†	–0.06	0.03
Satisfaction with Educational Video[1]	**0.45*****	**0.51*****	**0.46*****
Satisfaction with Information	**0.40*****	**0.42*****	**0.51*****
Dissatisfaction with Healthcare Provider Support[2]	–0.16†	–0.10	**–0.24*****
Decisional Conflict[1]	–0.12†	–0.06	–0.09
Perceived Risk[1]	0.10	0.12†	0.01
Communication Self-Efficacy[2]	**0.24***	0.13	**0.37*****
Anxiety[1]	–0.10	–0.12†	–0.12†
Depression[1]	–0.02	–0.07	–0.03
Genetic Testing Concerns[2]	0.08	0.08	–0.10

[a] = Association based on a t-test. All other associations are correlations.
[1] = Measure only captured in longitudinal study with Sample 1, $n = 226$.
[2] = Measure only captured in cross-sectional study with Sample 2, $n = 123$.
† $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

other demographic or cognitive factors, it was observed that the perceived utility for health and self factor was inversely associated with education. The confidence in secondary findings factor was positively associated with age and income, and inversely associated with dissatisfaction with healthcare provider support.

4. Discussion and conclusion

4.1. Discussion

We developed and conducted a preliminary validation of a novel measure to assess advanced cancer patients' perceived utility of secondary germline findings arising from TGP, a valuable and increasingly utilized test in precision oncology. Taken together, our results indicate that the final 16-item measure was well received and deemed intelligible by participants during its iterative creation, and is a valid instrument in samples of patients awaiting TGP results and those who received pathogenic/likely pathogenic secondary germline findings. Further, analyses support the ability of this measure to assess three distinct aspects of perceived utility: perceived utility for others, perceived utility for self and health, and confidence in secondary findings.

In developing this patient-reported measure, we aimed to capture a variety of ways in which secondary germline findings may have use, value, or implications for patients, consistent with empirical literature, conceptual frameworks, and our own research. Although the measure incorporated outcomes that may be conceptually mapped onto either the health and medicine-related aspects of clinical utility or the cognitive, behavioral, and social outcomes linked to definitions of personal utility [24-26], this dichotomy was not clearly reflected in the factor structure of the final measure. Rather, the target of the potential benefits—primarily divided between the patient themselves versus others including their families, doctors, and scientists—generally served as the distinguishing characteristic across the observed Factor 2 (perceived utility for self and health) and Factor 1 (perceived utility for others). This may reflect the unique context in which these patients are receiving genetic risk information; TGP's primary objective is to provide therapeutic insights and options, and patients may recognize that their advanced disease status means that their germline results will likely have differential implications for other individuals. Interestingly and contrary to our predictions, participants' health status was not significantly associated with any perceived utility factor. Whether this is due to the heterogenous types of "utility" included within each factor, or the fact that participants generally reported favorable functioning despite their advanced disease status, is unknown. It was also somewhat surprising that the results of the EFA indicated that item 1 ("My secondary findings will help reduce my family's chances of getting cancer") warranted deletion from the overall measure. There is a higher likelihood of clinical benefit for the family members of an advanced cancer patient than for the patient themselves in the setting where a pathogenic/likely pathogenic secondary germline finding is identified, and this item was generated with the intention of reflecting this reality. The poor performance of this item suggests several possibilities, including that patients may have different impressions of the meaning, likelihood, or ultimate consequences of their secondary germline findings; or that perhaps there is too much uncertainty associated with the necessary intervening steps (e.g., communication of the secondary germline findings to family, family uptake of cascade testing and receipt of a positive result for the familial mutation, and family adoption of risk-reducing strategies) that complicate anticipating a reduction in their family's cancer risk. Further work could explore these possibilities or the impact of alternative approaches to assessing such perceptions.

The third factor identified within this measure—confidence in secondary germline findings—does not clearly align with contemporary definitions of utility in genomic sequencing [24-26]. However, this factor and the component items, which assess the patient's trust in the accuracy of their secondary germline findings, confidence in their ability to understand these results, and ease in understanding them, address aspects of the interpretability and quality of the genetic risk information. These beliefs about the information itself theoretically serve as a necessary precondition to perceiving utility in secondary germline findings [23]. Future research may help clarify whether this factor is therefore better conceptualized as either a dimension of, or contributor to, perceived utility of secondary germline findings arising from TGP.

This measure may serve as a useful research tool for understanding patients' expectations and perceptions regarding the receipt and consequences of their secondary germline findings. Although limited, current research suggests that patients have high and potentially unrealistic expectations of TGP and associated secondary findings [62-64]. In the present study, knowledge about TGP and secondary germline findings was marginally associated with greater perceived utility for others, but was unrelated to the other perceived utility factors. Greater satisfaction with the educational video and information provided in the TGP consent process were strongly associated with all factors of perceived utility. Future work should explore how understanding of this process is related to patients' perceptions of utility, as well as the stability of these beliefs over time. Investigating how these perceptions may change in response to the receipt of positive and negative secondary germline findings (e.g., from expectations prior to TGP through evaluations of experienced utility), as well as the impact of potential discrepancies between these beliefs, is also warranted. Patients' expectations for sequencing outcomes can affect psychological and behavioral responses to those results and associated medical recommendations [34]. Patients may hesitate to follow or trust medical recommendations associated with unexpected results, which could lead to poorer outcomes. Thus, this patient-centered instrument may help to assess and

identify these cases, allowing for more personalized and effective care/counseling.

This measure may also aid communication processes. The American Society of Clinical Oncology (ASCO) Policy Statement specifies that oncology providers should communicate about the potential for secondary germline findings prior to TGP and assess patient preferences for receiving such information [65]. While this measure was not correlated with decisional conflict among the sample of participants assessed following consent to receipt of secondary germline findings from TGP, it may serve to facilitate informed and shared decision-making in this context. This measure may assist providers in these discussions by helping to identify a patient's expectations or motivations for consenting to the receipt of secondary findings, or highlighting potential concerns or future support needs (e.g., limited confidence in understanding the results). Future research could examine whether and how this tool could support patient-provider communication in the setting of decision-making regarding secondary germline findings from TGP. Further, we observed that perceived utility for others and confidence in secondary findings were both associated with greater self-efficacy for communicating one's secondary germline findings. Ensuring dissemination of these results to relatives is critical to allow for cascade testing and subsequent familial cancer prevention [66-68], and these utility beliefs may hold potential as targets for interventions to improve such communication.

4.2. Limitations

This study has several important limitations, including the validation of the measure in samples that are predominantly non-Hispanic white, college educated, and affluent. Further, our final measure exceeded the recommended 3rd-6th grade reading level for health-related materials [53,54]. Although this may not have been problematic given the educational background of many in our samples, this observation highlights both the difficulty in conveying genomic-related concepts in plain language and the need for additional work to expand the accessibility of research tools in this space. Additionally, most participants were in their 50s and 60s; younger patients may have different experiences regarding utility of secondary germline findings, such as children/family planning experiences. A large majority of the sample also had metastatic disease, consistent with the predominant use of TGP in patients with advanced disease [37,38]. Nonetheless, this limits the generalizability of the findings to the use of TGP in earlier stage disease, which will likely increase over time. Modification of the measure may be necessary to assess broader outcomes that may apply to patients with different prognoses. Finally, this measure focused primarily on beneficial implications of secondary germline findings, and therefore did not assess conceptually-relevant disutilities (e.g., stigma, distress) [26]; future research may examine whether and how evaluating such outcomes offers a more comprehensive assessment of the perceived utility of secondary germline findings from TGP.

4.3. Innovation

Secondary germline findings from TGP can provide important information about a patient's inherited risk for cancer and other diseases as well as impact health outcomes for their relatives. Understanding patient beliefs regarding the utility and accuracy of these results has the potential to offer insight into their subsequent decision-making, psychological reactions, and health behaviors. This patient-reported measure offers a new, validated tool to assess these beliefs, and to potentially contribute actionable information with respect to genetic counseling practices, patient-provider communication, or other clinical/educational interventions.

4.4. Conclusion

This work offers a novel validated measure for assessing advanced cancer patient's perceptions regarding the utility of secondary germline findings. Future research should confirm the psychometrics and validity of this measure in demographically and clinically diverse patients, and examine how these beliefs contribute to decision-making, as well as patient-provider and family communication processes, in precision oncology settings.

Funding

This work was supported by the Memorial Sloan Kettering Cancer Center Survivorship, Outcomes, and Risk Developmental Funds Award (PIs: J.G.H. and M.E.R.); by a Mentored Research Scholar Grants in Applied and Clinical Research, MRSG-16-020-01-CPPB, from the American Cancer Society (PI: J.G.H.); and by a National Institutes of Health Support Grant (NCI P30 CA008748).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

An immediate family member serves as a consultant in Ophthalmology for Adverum, Genentech, Gyroscope Therapeutics Limited, Neurogene, Optos Plc, Outlook Therapeutics, RegenexBio, and Regeneron outside the submitted work (Z.K.S.) - Patent pending on therapeutic applications of targeting ERCC3 mutations in cancer. Diagnosis and treatment of ercc3-mutant cancer US20210137850A1, and other relationship with AnaNeo Therapeutics, Inc (K.O) - Honoraria from Research to Practice, Intellisphere, Physicians' Education Resource, and MyMedEd; consulting or advisory for Artios Pharma (uncompensated), AstraZeneca (uncompensated), Change Healthcare, Daiichi-Sankyo (uncompensated), Epic Sciences (uncompensated), Merck (uncompensated), Pfizer (uncompensated), Tempus Lab (uncompensated), Zenith Pharma (uncompensated); other support from AstraZeneca (editorial services) and Pfizer (editorial services) (M.E.R.)

Acknowledgements

We wish to thank Elyse Shuk and Joy S. Westerman for their contributions to this research.

References

[1] Wolf SM, Lawrenz FP, Nelson CA, Kahn JP, Cho MK, Clayton EW, et al. Managing incidental findings in human subjects research: Analysis and recommendations. J Law Med Ethics. 2008.;36(2) 219-48, 211.
[2] Presidential Commission for the Study of Bioethical Issues. Anticipate and communicate: Ethical management of incidental and secondary findings in the clinical, research and direct-to-consumer contexts, Washington, DC; 2013.
[3] Schrader KA, Cheng DT, Joseph V, Prasad M, Walsh M, Zehir A, et al. Germline variants in targeted tumor sequencing using matched normal DNA. JAMA Oncol. 2016;2(1):104–11.
[4] Gray SW, Park ER, Najita J, Martins Y, Traeger L, Bair E, et al. Oncologists' and cancer patients' views on whole-exome sequencing and incidental findings: Results from the CanSeq study. Genet Med. 2016;18(10):1011–9.
[5] Gray SW, Hicks-Courant K, Lathan CS, Garraway L, Park ER, Weeks JC. Attitudes of patients with cancer about personalized medicine and somatic genetic testing. J Oncol Pract. 2012;8(6):329–35. 2 p following 335.
[6] Yushak ML, Han G, Bouberhan S, Epstein L, DiGiovanna MP, Mougalian SS, et al. Patient preferences regarding incidental genomic findings discovered during tumor profiling. Cancer. 2016;122(10):1588–97.
[7] Yusuf RA, Rogith D, Hovick SR, Peterson SK, Burton-Chase AM, Fellman BM, et al. Attitudes toward molecular testing for personalized cancer therapy. Cancer. 2015;121(2):243–50.
[8] Hamilton JG, Shuk E, Genoff MC, Rodriguez VM, Hay JL, Offit K, et al. Interest and attitudes of patients with advanced cancer with regard to secondary germline findings from tumor genomic profiling. J Oncol Pract. 2017;13(7):e590–601.
[9] Marron JM, DuBois SG, Glade Bender J, Kim A, Crompton BD, Meyer SC, et al. Patient/parent perspectives on genomic tumor profiling of pediatric solid tumors: the Individualized Cancer Therapy (iCat) experience, Pediatr. Blood Cancer. 2016;63(11):1974–82.
[10] Bijlsma RM, Wessels H, Wouters RHP, May AM, Ausems M, Voest EE, et al. Cancer patients' intentions towards receiving unsolicited genetic information obtained using next-generation sequencing. Fam Cancer. 2018;17(2):309–16.
[11] Best M, Butow P, Jacobs C, Juraskova I, Savard J, Meiser B, et al. Advanced cancer patient preferences for receiving molecular profiling results. Psychooncology. 2020;29(10):1533–9.

[12] Haddow JE, Palomaki GE. ACCE: A model process for evaluating data on emerging genetic tests. In: Khoury M, Little J, Burke W, editors. Human genome epidemiology: A scientific foundation for using genetic information to improve health and prevent disease. New York: Oxford University Press; 2003. p. 217–33.
[13] Hamilton JG, Edwards HM, Khoury MJ, Taplin SH. Cancer screening and genetics: A tale of two paradigms. Cancer Epidemiol Biomarkers Prev. 2014;23(6):909–16.
[14] Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): A policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19(2):249–55.
[15] Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565–74.
[16] Li MM, Chao E, Esplin ED, Miller DT, Nathanson KL, Plon SE, et al. Points to consider for reporting of germline variation in patients undergoing tumor testing: A statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(7):1142–8.
[17] Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1381–90.
[18] ACMG Board of Directors. ACMG policy statement: Updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. Genet Med. 2015;17(1):68–9.
[19] Roberts JS, Gornick MC, Le LQ, Bartnik NJ, Zikmund-Fisher BJ, Chinnaiyan AM, et al. Next-generation sequencing in precision oncology: Patient understanding and expectations. Cancer Med. 2019;8(1):227–37.
[20] Miller FA, Hayeems RZ, Bytautas JP, Bedard PL, Ernst S, Hirte H, et al. Testing personalized medicine: Patient and physician expectations of next-generation genomic sequencing in late-stage cancer care. Eur J Hum Genet. 2014;22(3):391–5.
[21] Foster MW, Mulvihill JJ, Sharp RR. Evaluating the utility of personal genomic information. Genet Med. 2009;11(8):570–4.
[22] Ravitsky V, Wilfond BS. Disclosing individual genetic results to research participants. Am J Bioeth. 2006;6(6):8–17.
[23] Bunnik EM, Janssens AC, Schermer MH. Personal utility in genomic testing: Is there such a thing? J Med Ethics. 2015;41(4):322–6.
[24] Kohler JN, Turbitt E, Biesecker BB. Personal utility in genomic testing: A systematic literature review. Eur J Hum Genet. 2017;25(6):662–8.
[25] Kohler JN, Turbitt E, Lewis KL, Wilfond BS, Jamal L, Peay HL, et al. Defining personal utility in genomics: A Delphi study. Clin Genet. 2017;92(3):290–7.
[26] Smith HS, Morain SR, Robinson JO, Canfield I, Malek J, Rubanovich CK, et al. Perceived utility of genomic sequencing: Qualitative analysis and synthesis of a conceptual model to inform patient-centered instrument development. Patient. 2022;15(3):317–28.
[27] Hayeems RZ, Luca S, Assamad D, Bhatt A, Ungar WJ. Utility of genetic testing from the perspective of parents/caregivers: A scoping review. Children (Basel). 2021.;8(4).
[28] Rohrmoser A, Pichler T, Letsch A, Westphalen CB, Keilholz U, Heinemann V, et al. Cancer patients' expectations when undergoing extensive molecular diagnostics-A qualitative study. Psychooncology. 2020;29(2):423–9.
[29] Clift KE, Halverson CM, Fiksdal AS, Kumbamu A, Sharp RR, McCormick JB. Patients' views on incidental findings from clinical exome sequencing. Appl Transl Genom. 2015;4:38–43.
[30] Halverson CM, Clift KE, McCormick JB. Was it worth it? Patients' perspectives on the perceived value of genomic-based individualized medicine. J Community Genet. 2016;7(2):145–52.
[31] O'Connor AM, Tugwell P, Wells GA, Elmslie T, Jolly E, Hollingworth G, et al. A decision aid for women considering hormone therapy after menopause: Decision support framework and evaluation. Patient Educ Couns. 1998;33(3):267–79.
[32] Hoefel L, O'Connor AM, Lewis KB, Boland L, Sikora L, Hu J, et al. 20th anniversary update of the Ottawa Decision Support Framework Part 1: A systematic review of the decisional needs of people making health or social decisions. Med Decis Making. 2020;40(5):555–81.
[33] Stacey D, Légaré F, Boland L, Lewis KB, Loiselle M-C, Hoefel L, et al. 20th anniversary Ottawa Decision Support Framework: Part 3 overview of systematic reviews and updated framework. Med Decis Making. 2020;40(3):379–98.
[34] Khan CM, Rini C, Bernhardt BA, Roberts JS, Christensen KD, Evans JP, et al. How can psychological science inform research about genetic counseling for clinical genomic sequencing? J Genet Couns. 2015;24(2):193–204.
[35] Lord C, Taylor C. Biased assimilation: Effects of assumptions and expectations on the interpretation of new evidence. Soc Person Psychol Compass. 2009;3:827–41.
[36] Sweeny K, Ghane A, Legg AM, Huynh HP, Andrews SE. Predictors of genetic testing decisions: A systematic review and critique of the literature. J Genet Couns. 2014;23(3):263–88.
[37] Tripathy D, Harnden K, Blackwell K, Robson M. Next generation sequencing and tumor mutation profiling: Are we ready for routine use in the oncology clinic? BMC Med. 2014.;12(140).
[38] Parsons DW, Roy A, Plon SE, Roychowdhury S, Chinnaiyan AM. Clinical tumor sequencing: An incidental casualty of the American College of Medical Genetics and Genomics recommendations for reporting of incidental findings. J Clin Oncol. 2014;32(21):2203–5.
[39] Turbitt E, Kohler JN, Angelo F, Miller IM, Lewis KL, Goddard KA, et al. The PrU: Development and validation of a measure to assess personal utility of genomic results. Genet Med. 2022. https://pubmed.ncbi.nlm.nih.gov/36516964/.
[40] Rothrock NE, Kaiser KA, Cella D. Developing a valid patient-reported outcome measure. Clin Pharmacol Ther. 2011;90(5):737–42.
[41] Biesecker LG, Mullikin JC, Facio FM, Turner C, Cherukuri PF, Blakesley RW, et al. The ClinSeq project: Piloting large-scale genome sequencing for research in genomic medicine. Genome Res. 2009;19(9):1665–74.
[42] Cragun D, Malo TL, Pal T, Shibata D, Vadaparampil ST. Colorectal cancer survivors' interest in genetic testing for hereditary cancer: Implications for universal tumor screening. Genet Test Mol Biomarkers. 2012;16(6):493–9.
[43] Won HH, Scott SN, Brannon AR, Shah RH, Berger MF. Detecting somatic genetic alterations in tumor specimens by exon capture and massively parallel sequencing. J Vis Exp. 2013;80:e50710.
[44] Cheng DT, Mitchell TN, Zehir A, Shah RH, Benayed R, Syed A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. J Mol Diagn. 2015;17(3):251–64.
[45] Willis GB. Cognitive interviewing: A tool for improving questionnaire design. Thousand Oaks, CA: Sage Publications; 2005.
[46] Brod M, Tesler LE, Christensen TL. Qualitative research and content validity: Developing best practices based on science and experience. Qual Life Res. 2009;18(9):1263–78.
[47] US Department of Health and Human Services Food and Drug Administration. Guidance for industry patient-reported outcome measures: Use in medical product development to support labeling claims; 2009.
[48] Green J, Thorogood N. Qualitative methods for health research. London, UK: Sage Publications; 2004.
[49] Miles MB, Huberman AM, Saldana J. Qualitative data analysis: A methods sourcebook. Thousand Oaks, CA: Sage Publications; 2014.
[50] Saldana J. The coding manual for qualitative researchers. London, UK: Sage Publications; 2009.
[51] Patton MQ. Qualitative research and evaluation methods. Thousand Oaks, CA: Sage Publications; 2002.
[52] Kincaid JP, Fishburne Jr RP, Rogers RL, Chissom BS. Derivation of New Readability Formulas (Automated Readability Index, Fog Count and Flesch Reading Ease Formula), for Navy Enlisted Personnel. Fort Belvoir, VA: Defense Technical Information Center; 1975.
[53] Weiss BD. Health literacy and patient safety: Help patients understand. Manual for clinicians. 2nd ed. Chicago: American Medical Association Foundation; 2007.
[54] National Institutes of Health.. Clear and simple. https://www.nih.gov/institutes-nih/nih-office-director/office-communications-public-liaison/clear-communication/clear-simple; 2021.
[55] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649–56.
[56] National Cancer Institute.. HINTS: Health Information National Trends Survey. http://hints.cancer.gov/.
[57] O'Connor AM. User manual - Decisional Conflict Scale (16 item statement format); 2010.
[58] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67(6):361–70.
[59] Traino HM. Communication self-efficacy, perceived conversational difficulty, and renal patients' discussions about transplantation. Patient Educ Couns. 2014;94(2):180–6.
[60] Cella D, Hughes C, Peterman A, Chang CH, Peshkin BN, Schwartz MD, et al. A brief assessment of concerns associated with genetic testing for cancer: The Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. Health Psychol. 2002;21(6):564–72.
[61] Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Modeling. 1999;6(1):1–55.
[62] Shirdarreh M, Aziza O, Pezo RC, Jerzak KJ, Warner E. Patients' and oncologists' knowledge and expectations regarding tumor multigene next-generation sequencing: A narrative review. Oncologist. 2021;26(8):e1359–71.
[63] Smith-Uffen M, Bartley N, Davies G, Best M. Motivations and barriers to pursue cancer genomic testing: A systematic review. Patient Educ Couns. 2021;104(6):1325–34.
[64] Wolyniec K, Sharp J, Lazarakis S, Mileshkin L, Schofield P. Understanding and information needs of cancer patients regarding treatment-focused genomic testing: A systematic review. Psychooncology. 2020;29(4):632–8.
[65] Robson ME, Bradbury AR, Arun B, Domchek SM, Ford JM, Hampel HL, et al. American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2015;33(31):3660–7.
[66] Offit K, Tkachuk KA, Stadler ZK, Walsh MF, Diaz-Zabala H, Levin JD, et al. Cascading after peridiagnostic cancer genetic testing: An alternative to population-based screening. J Clin Oncol. 2020;38(13):1398–408.
[67] Menko FH, Ter Stege JA, van der Kolk LE, Jeanson KN, Schats W, Moha DA, et al. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: A systematic review of the literature and implications for clinical practice. Fam Cancer. 2019;18(1):127–35.
[68] Roberts MC, Dotson WD, DeVore CS, Bednar EM, Bowen DJ, Ganiats TG, et al. Delivery of cascade screening for hereditary conditions: A scoping review of the literature. Health Aff (Millwood). 2018;37(5):801–8.