2002

Psychological impact of comprehensive tumor genomic profiling results for advances cancer patients

Phyllis N. Butow

Megan Best

Grace Davies

Timothy Schlub

Christine Napier

See next page for additional authors

This article was originally published as:
Butow, P. N., Best, M., Davies, G., Schlub, T., Napier, C., Bartley, N., Ballinger, M., Juraskova, I., Meiser, B., Goldstein, D., Biesecker, B., & Thomas, D. (2002). Psychological impact of comprehensive tumor genomic profiling results for advances cancer patients. *Patient Education and Counseling, 105* (7), 2206-2216.

Original article available here:
10.1016/j.pec.2022.01.011

Authors

Phyllis N. Butow, Megan Best, Grace Davies, Timothy Schlub, Christine Napier, Nicci Bartley, Mandy Ballinger, Ilona Juraskova, Bettina Meiser, David Goldstein, Barbara Biesecker, and David Thomas

This is the accepted manuscript version of an article published as:

Butow, P.N., Best, M.C., Davies, G., Schlub, T., Napier, C.E., Bartley, N., Ballinger, M.L., Juraskova, I., Meiser, B., Goldstein, D., Biesecker, B., & Thomas, D.M. (2022). Psychological impact of comprehensive tumor genomic profiling results for advances cancer patients. *Patient Education and Counseling 105*(7) 2206-2216.
https://doi.org/10.1016/j.pec.2022.01.011

This article has been published in its final form at:
https://doi.org/10.1016/j.pec.2022.01.011

Patient Education and Counseling xxx (xxxx) xxx

Contents lists available at ScienceDirect

Patient Education and Counseling

journal homepage: www.journals.elsevier.com/patient-education-and-counseling

Psychological impact of comprehensive tumor genomic profiling results for advanced cancer patients

Phyllis N. Butow [a,*], Megan C. Best [a], Grace Davies [a], Timothy Schlub [b], Christine E. Napier [c], Nicci Bartley [a], Mandy L. Ballinger [c,d], Ilona Juraskova [e], Bettina Meiser [f], David Goldstein [g], Barbara Biesecker [h], David M. Thomas [c,d], members of the PiGeOn Project

[a] Psycho-Oncology Co-operative Research Group (PoCoG), Level 6 (North) Lifehouse (C36Z), School of Psychology, University of Sydney, Sydney 2006 Australia
[b] School of Public Health, University of Sydney, 2006 Sydney, Australia
[c] Cancer Theme, Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, NSW 2010, Australia
[d] St Vincent's Clinical School, University of NSW, Sydney, Australia
[e] School of Psychology, University of Sydney, Sydney 2006, Australia
[f] Psychosocial Research Group, Prince of Wales Clinical School, University of NSW, Sydney 2052, Australia
[g] Dept of Medical Oncology, Prince of Wales Hospital, 320-346 Barker St, Randwick, NSW 2031, Australia
[h] Newborn Screening, Ethics and Disability Studies, RTI International, Washington, DC, USA

ARTICLE INFO

Keywords:
Psychological outcomes
Genomics
Comprehensive tumor genomic profiling

ABSTRACT

Objective: Comprehensive tumor genomic profiling (CTGP) is increasingly used to personalize treatments, providing hope, but potentially disappointment, for patients. We explored psychological outcomes in patients with advanced, incurable cancer, after receiving CTGP results.

Methods: Participants with advanced, incurable cancer (n = 560, mean age 56, 43% university educated) in this longitudinal substudy of the Molecular Screening and Therapeutics Program (MoST), completed questionnaires before and after receiving CGP results. MoST participants, recruited from Australian oncology clinics, undergo CTGP, and if there are actionable findings, are offered treatment in a related therapeutic trial if available.

Results: Patients who received actionable results, (n = 356, 64%) had lower gene-related distress (MICRA) ($p < 0.001$) and Impact of Events scores ($p = 0.039$) than patients with non-actionable results. Those with actionable results offered ensured access to tailored treatment (n = 151) reported lower anxiety ($p = 0.002$) and depressive symptoms ($p = 0.01$) and greater hope ($p = 0.002$) than those not offered. Positive attitudes towards uncertainty and higher self-efficacy for coping with results were associated with lower psychological distress and uncertainty, and higher hope and satisfaction with the decision to have CTGP (*ps*=0.001–0.047). Those with higher knowledge reported greater anxiety ($p = 0.034$).

Conclusion: Receiving a non-actionable CTGP result, or an actionable result without ensured access to treatment, may cause increased distress in advanced cancer patients. Coping style was also associated with distress.

Practice implications: Pre-testing assessment and counseling addressing attitudes toward uncertainty and self-efficacy, and post-CTGP result support for patients receiving a non-actionable result or who receive an actionable results without ensured access to treatment, may benefit patients.

1. Introduction

Understanding the molecular basis of cancer is a focus of current research. With improved technology, the utility of comprehensive tumor genomic profiling (CTGP: laboratory analysis of tumor tissue to identify driver mutations in cancer) to guide prognostication and personalized treatment for advanced cancer is expanding [1]. CTGP can identify somatic variants that: i) can guide personalized treatment targeting the specific mutation found (clinically actionable); ii) do not affect treatment (non-actionable); or iii) are of uncertain therapeutic potential. CTGP can be followed by further confirmatory testing if it is suspected that gene variants may have a germline (heritable) origin (and therefore may also be relevant to the patient's family).

Although estimates of the rates of clinical actionability are

* Correspondence to: Level 6 North, Lifehouse C39Z, University of Sydney, NSW 2006, Australia.
E-mail address: phyllis.butow@sydney.edu.au (P.N. Butow).

https://doi.org/10.1016/j.pec.2022.01.011
Received 6 June 2021; Received in revised form 16 January 2022; Accepted 21 January 2022
Available online 24 January 2022

Table 1
Description of study measures, assessment timepoints and internal consistency.

Measure	**T0** Baseline	**T1** Post result receipt
Clinical characteristics: were available through the MoST database and included previous visit to a family cancer clinic, previous genetic testing, personal and family history of cancer, rarity of cancer, time since diagnosis, and ECOG performance status.		
Demographic characteristics: were also available through the MoST database and included gender, age, education level, occupation, marital status, parental status, language spoken at home, socio-economic status (Socio-Economic Indexes for Areas – SEIFA- calculated from postcode), and urban versus rural residence (Accessibility and Remoteness Index of Australia - ARIA).		
Self-Efficacy: Four items adapted from Rosenberg et al., [17] assessed perceived ability to cope with CTGP results. Response options are on a Likert-scale ranging from "strongly disagree" to "strongly agree" (scores range 1–5). High scores indicate greater perceived ability to cope.	X	
Attitude to Uncertainty: The 7-item Attitude towards Uncertainty scale [18] measures attitudes towards uncertainty in a medical testing context. Items are rated on a Likert-scale ranging from "strongly disagree" to "strongly agree" (scores range 1–5). High scores indicate a more negative attitude towards uncertainty.	X	
Knowledge: At the time the study was planned no alternative validated knowledge scale existed, so we used a study-developed measure. An eight-item, multiple choice, study-developed questionnaire assessed knowledge of the purpose of CTGP, likely frequency of informative results, cancers in which informative results are more likely to be found, its utility in guiding treatment and understanding future cancer risk. Scores are averaged (average number of items correct, possible range 0–100%). High scores indicate greater knowledge.	X	
Coping with genetic test results: The 25-item Multidimensional Impact of Cancer Risk Assessment (MICRA) [19] assesses impact of result disclosure after genetic testing. The patient rates feelings over the past week. The MICRA has three subscales: distress, uncertainty and positive experience. Items are rated on a scale ranging from "never" to "often". Items are summed with possible values ranging from 0 to 95. High scores indicate poorer outcomes.		X
Cancer specific anxiety: The Impact of Events Scale (IES) [20] assesses the frequency of cancer-related anxiety in relation to CTGP results. The IES is comprised of two subscales, intrusive thinking and avoidance. Items are rated on a scale ranging from "not at all" to "often". Items are summed with possible values ranging from 0 to 75. High scores indicate greater cancer-related anxiety.		X
General anxiety and depression: The 14-item Hospital Anxiety and Depression Scale (HADS), [18] comprises two seven-item sub-scales, one for anxiety and the other depression. Items are summed with possible values for each subscale ranging from 0 to 21. High subscale scores indicate greater morbidity.		X
Satisfaction with CTGP decision: The six-item Satisfaction with Decision scale [22] measures satisfaction with decision to have CTGP Items are rated on a Likert-scale, from "strongly disagree" to "strongly agree". Items are summed, ranging from 0 to 30. High scores indicate greater satisfaction.		X
Decisional conflict: The 10-item version of the Decisional Conflict Scale (DCS) [20] comprises five subscales measuring: 1) uncertainty, 2) feelings of being uninformed, 3) clarity of values, 4) sense of being unsupported in decision-making, and 5) evaluation of the quality of the decision. Possible values range from 0 to 100. High scores indicate greater decisional conflict.		X
Hope: The 12-item Herth Hope Index (HHI) [21] comprises three subscales measuring: 1) inner sense of temporality and future, 2) inner positive readiness and expectancy, and 3) inner connectedness with self and others. Items are rated on a Likert-scale, from "strongly disagree" to "strongly agree" e.g. "I have a positive outlook towards life". Items are summed, ranging from 0 to 48. High scores indicate greater hope.		X

progressively rising from 10% to 40%, [2] to date more than half of all patients undergoing CTGP have received a non-actionable result. Moreover, drug access remains challenging, such that fewer than half of those who receive an actionable result will go onto treatment. [3] CTGP results are not simple to interpret, potentially identifying variants with uncertain therapeutic potential and occasionally, variants with a germline origin (with relevance to the patient's family). Thus, CTGP can engender significant uncertainty, with the associated potential for significant distress. Patients report struggling to understand, process and assess how to act on results. [4].

Accordingly, concern exists among the genetic and oncology communities that cancer patients may experience detrimental psychological consequences from receipt of genomic results [5]. Few relevant studies have focused on tumor CTGP in cancer, as noted in a recent systematic review of psychological outcomes of genomic testing [6].

A survey [7] of children (if > age 18) with relapsed, refractory, high risk solid tumors who had recently received results from CTGP, or their parents if < age 18, found that no respondents reported regretting having CTGP, or that they/their child had been hurt or suffered additional anxiety or stress as a result of CTGP. However, a greater percentage of participants had hoped that participating would provide them/their child with more treatment options than eventuated (72% versus 27%, $p < 0.001$). However, it is unclear how these results would generalize to an adult advanced cancer population. Similarly, Biesecker et al., [8] studying responses to genomic uncertainty, reported that participants expressed disappointment and feelings of perplexity and anxiety at having received uncertain information, and felt less hopeful. Thus genomic results can engender reduced hope, anxiety, disappointment, and potentially in patients with advanced cancer, depression.

A number of theoretical frameworks can frame our understanding of how participants respond to threatening and uncertain health information. Uncertainty in Illness Theory [9] suggests those with negative attitudes towards uncertainty will cope less well with genomic results than those who view uncertainty as an opportunity. Newson et al. [10], building on previous adaptations of Uncertainty in Illness Theory for the genomics context [11,12], note that responses to the probabilistic, ambiguous or complexity uncertainty inherent to information arising from genomics testing, can be influenced by the provider's or recipient's views on and uses of it.

Social Cognitive Theory [13] suggests that people who have greater confidence in their ability to cope (high perceived self-efficacy) experience less distress under stressful conditions. A recent meta-analysis of 108 studies showed a strong negative relationship between perceived self-efficacy and distress in cancer patients [14]. However, neither construct has been explored to date in relation to receipt of CTGP results. Finally, if patients have a good understanding of the CTGP process and outcomes, we anticipate they will cope more effectively with their results. Framed by these theories, our study aimed to assess psychological responses in advanced cancer patients who had recently received CTGP results. Based on Newson et al.'s conception of uncertainty in genomics [10], and the psychological outcomes documented in previous studies [7,8] we first hypothesized that the added utility of actionable results, and the reduction in uncertainty associated with a definite course of consequent action, would lead to improved psychological outcomes:

We hypothesized that:

Patients who received actionable results would report lower levels of genomics-specific and general anxiety and depression symptoms, less uncertainty, more hope and higher satisfaction with the decision to have CTGP, than those whose result was non-actionable.

Among those receiving an actionable result, participants recommended treatment within the research setting would report lower levels of genomics-specific and general anxiety and depression symptoms, less uncertainty, greater hope, and higher satisfaction

with the decision to have CTGP, than those facing uncertain access to targeted treatment through their oncologist. This relationship would be strongest in those receiving non-actionable results.

Based on the role of coping and understanding noted in Uncertainty in Illness Theory, and Social Cognitive Theory, we further hypothesized that:

Patients who had more positive attitudes toward uncertainty, high self-efficacy for coping with results and better knowledge of CTGP and its potential outcomes would report lower levels of genomics-specific and general anxiety and depression symptoms, less uncertainty, greater hope, and higher satisfaction with the decision to have CTGP, than those with negative attitudes towards uncertainty, lower self-efficacy and poorer knowledge.

2. Methods

2.1. Participants

The Molecular Screening and Therapeutics (MoST) Program [15] is recruiting adult participants with pathologically confirmed advanced or metastatic solid cancers with a focus on rare and less common cancers. Participants undergo CTGP, and if there are actionable findings, are offered treatment in a related therapeutic trial if available. The MoST Program eligibility criteria require participants to: be receiving or having completed their last line of effective therapy; have Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1 or 2; and have sufficient accessible tissue for molecular profiling. Participants have been recruited to the MoST Program from tertiary oncology units in hospitals throughout Australia from 2016 (ongoing). Interested patients meet with a researcher face-to-face or via phone to receive information about the study and give written consent. At that time they elect to receive or not, information on hereditary cancer risks of potential importance to their future health, or that of their blood relatives (germline results). The patient's permission is not sought to receive the molecular variants detected in the tumor.

CTGP results are reviewed by a Molecular Tumor Board. Actionable results include molecular variants for which there is treatment available, that targets the variant and for which there is clinical or preclinical evidence of anti-cancer activity. Such treatment is offered either through a MoST substudy (ensured access) or via another route through their oncologist (which may take some time to organize or be unavailable at the patient's treating institution). Non-actionable results include molecular variants without linked treatment recommendations (that is, to date, there is no anti-cancer treatment available which targets that molecular variant). Participants are notified of results approximately 11 weeks after consent by their oncologist, who receives a detailed report from the research team.

The Psychosocial Issues in Genomics in Oncology (PiGeOn) Project is a longitudinal, mixed- methods psychosocial substudy of MoST, which aims to examine the psychosocial, behavioral and ethical impact of CTGP [16]. Participants gave written consent to participate in PiGeOn while consenting to participate in MoST.

2.2. Data collection

PiGeOn participants completed questionnaires at consent (baseline T0), within 1 week of receiving CTGP results (T1), and at two months following receipt of results (T2). Demographic and disease details were collected by the MoST Program. We report data collected at T1, with baseline data utilized in predictive analyses.

The T0 questionnaire (see Table 1) included items assessing self-efficacy to cope with CTGP results, [17] the Attitude towards Uncertainty scale [18] and a study-developed questionnaire assessing knowledge of CTGP. The T1 questionnaire included the Multidimensional Impact of Cancer Risk Assessment (MICRA), [19] Impact of Events Scale (IES), [20] Hospital Anxiety and Depression Scale (HADS), [21] Satisfaction with Decision scale, [22] and Herth Hope Index (HHI) [23].

2.3. Sample size and data analysis

The power calculation for this study was provided in the protocol paper. [16] In summary, assuming 15% of patients receive an actionable result and using a significance level of 0.05, 470 participants would have 90% power to detect a mean change of 5.8 and 2.6 points on the Impact of Events scale for patients with actionable and non-actionable results respectively and capacity to include 24 explanatory variables in regression analyses. Thus with 560 participants we had more than enough power for these analyses. Mean differences in outcomes were compared using *t*-tests, chi-squared tests or non-parametric as appropriate. Multiple regression was used to adjust for confounders and identify predictors of outcomes. Analyses were undertaken using IBM SPSS Statistics Version 25. Missing data was handled in the regression using complete case analysis. Assumptions of normality of residuals and

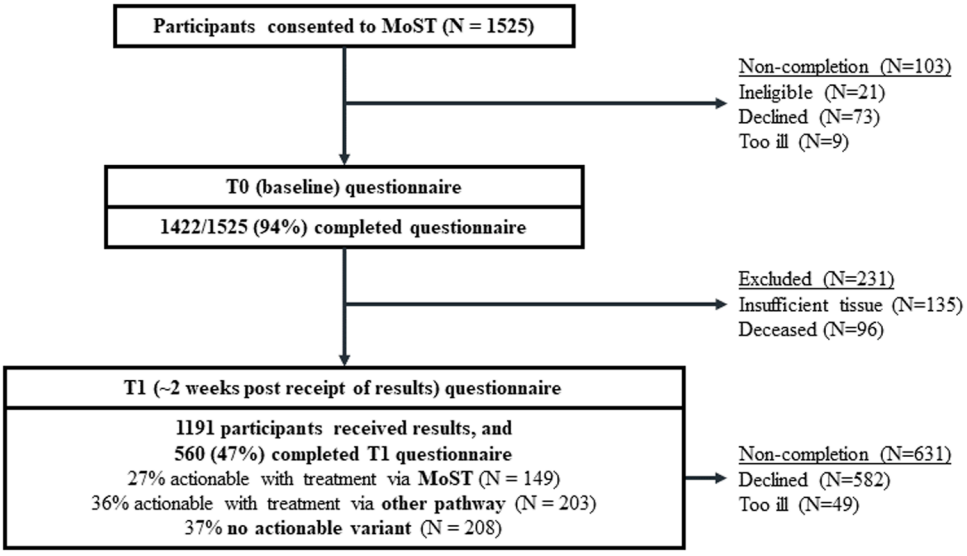

Fig. 1. Participant flow through study.

Table 2
Demographics and psycho-social descriptives.

	Treatment via MoST substudy (N = 151)	Treatment via other pathway (N = 205)	Non-actionable variant (N = 204)	Total sample (N = 560)
Sex				
Female	80 (53%)	111 (54%)	114 (56%)	305 (54%)
Male	71 (47%)	94 (46%)	90 (44%)	255 (46%)
Age				
Mean (SD)	55.21 (15.08)	57.22 (13.79)	56.30 (13.29)	56.34 (13.97)
Median (IQR)	57 (26)	59 (16)	58.50 (19.75)	58.50 (20.75)
Range	20–82	21–88	18–89	18–89
Highest level of education				
Primary school (some or all)	1 (0.6%)	2 (1%)	2 (1%)	5 (0.9%)
Secondary school - year 7 or 8	2 (1%)	7 (3%)	9 (4%)	18 (3%)
Secondary school - year 9 or 10	25 (17%)	38 (19%)	39 (19%)	102 (18%)
Secondary school - year 11 or 12	26 (17%)	26 (13%)	27 (13%)	79 (14%)
Vocational training	24 (16%)	36 (18%)	44 (22%)	104 (19%)
University did not graduate	8 (5%)	1 (0.5%)	1 (0.5%)	10 (2%)
University graduated	65 (43%)	93 (46%)	82 (40%)	240 (43%)
Missing	0	2 (1%)	0	2 (0.4%)
Speaks a language other than English				
Yes	23 (15%)	24 (12%)	36 (18%)	83 (15%)
No	128 (85%)	181 (88%)	168 (82%)	477 (85%)
Parental status				
Yes, has children	118 (79%)	154 (75%)	169 (83%)	441 (79%)
No	31 (21%)	50 (25%)	34 (17%)	115 (21%)
Missing	2 (1%)	1 (0.5%)	1 (0.5%)	4 (0.7%)
ECOG				
Mean (SD)	0.46 (0.55)	0.44 (0.54)	0.48 (0.55)	0.46 (0.54)
Range	0–2	0–2	0–2	0–2
Accessibility and Remoteness Index of Australia (ARIA)				
Urban	138 (91%)	181 (88%)	184 (90)	503 (90%)
Remote	12 (8%)	24 (12%)	20 (10%)	56 (10%)
Unknown/overseas	1 (0.7%)	0	0	1 (0.2%)
Medical/science occupation				
Yes	5 (3%)	22 (11%)	15 (7%)	42 (8%)
No	146 (97%)	183 (89%)	189 (93%)	518 (93%)
Visited a family cancer clinic				
Yes	18 (12%)	28 (14%)	18 (9%)	64 (11%)
No	131 (87%)	171 (83%)	177 (87%)	479 (86%)
Don't know	1 (0.7%)	6 (3%)	9 (4%)	16 (3%)
Missing	1 (0.7%)	0	0	1 (0.2%)
Time since diagnosis (years)				
Mean (SD)	4.07 (6.10)	4.48 (6.16)	3.42 (4.62)	3.98 (5.64)
Range	0.03–40.25	0–42	0.05–31.58	0–42
Cancer incidence				
Common (>12/100,00 population)	24 (16%)	50 (25%)	31 (15%)	105 (19%)
Less Common (6–12/100,000 population)	20 (13%)	25 (12%)	20 (10%)	65 (12%)
Rare (<6/100,000 population)	107 (71%)	129 (63%)	153 (75%)	389 (70%)
Missing	0	1 (0.5%)	0	1 (0.2%)
Cancer type				
Bone and soft tissue	48 (32%)	28 (14%)	62 (30%)	138 (25%)
Brain	13 (9%)	31 (15%)	14 (7%)	58 (10%)
Colorectal	14 (9%)	21 (10%)	15 (7%)	50 (9%)
Pancreatic	15 (10%)	12 (6%)	18 (9%)	45 (8%)
Ovarian	6 (4%)	12 (6%)	17 (8%)	35 (6%)
Other	55 (36%)	101 (49%)	78 (38%)	234 (42%)
Previous genetic testing				
Yes	32 (21%)	47 (23%)	33 (16%)	112 (20%)
No	113 (74%)	156 (76%)	164 (81%)	433 (78%)
Don't know	7 (5%)	1 (0.5%)	6 (3%)	14 (3%)
Missing	0	1 (0.5%)	1 (0.5%)	2 (0.4%)
Self-efficacy to cope with results (T0)				
Mean (SD)	4.34 (0.62)	4.40 (0.65)	4.30 (0.66)	4.35 (0.65)
Range	2–5	1–5	1–5	1–5
Missing	2 (1%)	0	0	2 (0.4%)
Attitude towards uncertainty (T0)				
Mean (SD)	4.40 (0.53)	4.40 (0.55)	4.33 (0.55)	4.38 (0.54)
Range	2.83–5	1.5–5	1.43–5	1.43–5
Knowledge	**N = 81**	**N = 182**	**N = 180**	**N = 443**
Mean (SD)	44.14% (21.57%)	46.91% (18.81%)	41.67% (19.64%)	44.27% (19.77%)
Range	0–75%	0–75%	0–75%	0–75%
HADS (Anxiety)				
Mean (SD)	6.18 (4.22)	7.20 (4.60)	7.13 (4.08)	6.90 (4.33)
Range	0–17	0–20	0–19	0–20
Above clinical cut-off for 'normal' (≥8)	50 (34%)	82 (41%)	84 (42%)	216 (39%)

(*continued on next page*)

Table 2 (*continued*)

	Treatment via MoST substudy (N = 151)	**Treatment via other pathway (N = 205)**	**Non-actionable variant (N = 204)**	**Total sample (N = 560)**
Above the mean score	63 (43%)	82 (41%)	84 (42%)	277 (50%)
Missing	3 (2%)	3 (1%)	4 (2%)	10 (2%)
HADS_Depression				
Mean (SD)	4.47 (3.87)	5.36 (4.15)	5.02 (3.55)	5.00 (3.87)
Range	0–18	0–21	0–18	0–21
Above clinical cut-off for 'normal' (≥8)	31 (21%)	55 (27%)	43 (22%)	129 (23%)
Above the mean score	59 (40%)	86 (43%)	77 (39%)	213 (39%)
Missing	3 (2%)	3 (1%)	4 (2%)	10 (2%)
HADS_Total				
Mean (SD)	10.65 (7.31)	12.56 (8.09)	12.15 (6.82)	11.90 (7.46)
Range	0–29	0–39	0–36	0–39
Missing	3 (2%)	3 (2%)	4 (2%)	10 (2%)
MICRA_Distress				
Mean (SD)	6.08 (6.35)	6.16 (7.08)	8.19 (6.83)	6.89 (6.87)
Range	0–26	0–28	0–30	0–30
Missing	5 (3%)	1 (0.5%)	0	6 (1%)
MICRA_Uncertainty				
Mean (SD)	13.98 (8.49)	13.82 (8.79)	15.60 (8.24)	14.52 (8.54)
Range	0–40	0–41	0–38	0–41
Missing	5 (3%)	1 (0.5%)	0	6 (1%)
MICRA Positive Experience (Reverse scored)				
Mean (SD)	4.84 (3.82)	5.84 (4.59)	8.80 (4.30)	6.67 (4.60)
Range	0–15	0–20	0–20	0–20
Missing	5 (3%)	1 (0.5%)	0	6 (1%)
MICRA_Total				
Mean (SD)	24.91 (15.07)	25.83 (15.97)	32.59 (14.40)	28.08 (15.53)
Range	0–76	1–78	0–74	0–78
Missing	5 (3%)	1 (0.5%)	0	6 (1%)
Decisional Conflict Scale				N = 356
Mean (SD)	25.11 (23.32)	24.04 (22.21)	NA	24.56 (22.71)
Range	0–100	0–80		0–100
Missing	21 (14%)	64 (31%)		85 (24%)
Satisfaction with Decision				
Mean (SD)	26.54 (4.18)	26.18 (4.89)	25.34 (4.46)	25.97 (4.57)
Range	6–30	6–30	6–30	6–30
Missing	2 (1%)	4 (2%)	5 (2%)	11 (2%)
Impact of Events_Intrusion				
Mean (SD)	3.61 (5.57)	4.41 (6.59)	5.19 (6.81)	4.48 (6.43)
Range	0–31	0–33	0–35	0–35
Missing	1 (0.7%)	3 (1%)	4 (2%)	8 (1%)
Impact of Events_Avoidance				
Mean (SD)	5.63 (7.57)	6.28 (8.34)	8.46 (9.32)	6.89 (8.59)
Range	0–31	0–33	0–36	0–36
Missing	1 (0.7%)	3 (1%)	4 (2%)	8 (1%)
Impact of Events_Overall				
Mean (SD)	9.24 (12.3)	10.69 (14.06)	13.72 (14.82)	11.39 (13.99)
Range	0–53	0–58	0–55	0–58
Proportion in clinical range (≥8)	57 (38%)	83 (41%)	104 (52%)	251 (46%)
Proportion above mean	45 (30%)	67 (33%)	79 (40%)	197 (36%)
Missing	1 (0.7%)	3 (1%)	5 (2%)	9 (2%)
Herth Hope Index_Inner sense of temporality and future	**N = 106**	**N = 201**	**N = 198**	**N = 505**
Mean (SD)	12.67 (2.31)	12.26 (2.29)	11.93 (2.29)	12.22 (2.31)
Range	6–16	4–16	7–16	4–16
Missing	0	4 (2%)	3 (2%)	7 (1%)
Herth Hope Index_Inner positive readiness and expectancy				
Mean (SD)	13.84 (1.82)	13.16 (1.92)	13.11 (1.96)	13.28 (1.94)
Range	8–16	5–16	7–16	5–16
Missing	0	4 (2%)	3 (2%)	7 (1%)
Herth Hope Index_Inner connectedness with self and others				
Mean (SD)	13.45 (2.07)	12.73 (2.12)	12.92 (2.10)	12.96 (2.11)
Range	7–16	4–16	5–16	4–16
Missing	0	4 (2%)	3 (1%)	7 (1%)
Herth Hope Index_Total				
Mean (SD)	39.96 (5.42)	38.15 (5.69)	37.95 (5.77)	38.46 (5.71)
Range	24–48	13–48	21–48	13–48
Missing	0	4 (2%)	3 (1%)	7 (1%)

homogeneity of variance were checked visually through diagnostic residual plots. Multivariable models were constructed with the inclusion of all potential confounders, and those predictors that showed at least weak evidence for an association with the outcome in univariate analysis. Collinear independent variables were identified and removed.

This study was approved by the St Vincent's Hospital Human Research Ethics Committee, Reference number HREC/16/SVH/23.

Table 3
Summary of significant results from linear regression analysis – hypothesis 1: actionable (n = 356) vs non-actionable (n = 204).

	Satisfaction with Decision		MICRA TOTAL		MICRA_Uncertainty	HADS_Anxiety		HADS_Depression		Impact of Events Scale		Hope Herth Index	
Independent variables	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**
Sex	-0.33 (−1.11 to 0.46)	.413	1.23 (−1.32 to 3.78)	.345	1.37 (−0.03 to 2.78)	.056	0.66 (−0.07 to 1.39)	.077	-0.38 (−1.03 to 0.28)	.257	0.49 (−1.82 to 2.81)	.677	0.21 (−0.80 to 1.23)	.680
Age (for every 10-year increase)	-0.02 (−0.33 to 0.28)	.882	-1.11 (−2.10 to −0.12)	.028	-0.73 (−0.13 to −0.19)	**.009**	-0.54 (−0.83 to −0.26)	**< .001**	-0.23 (−0.48 to 0.03)	.080	-0.22 (−1.12 to 0.68)	.632	0.47 (0.07–0.86)	**.021**
Education	0.08 (−0.15 to 0.32)	.447	-0.63 (−1.38 to 0.12)	.101	-0.49 (−0.91 to −0.08)	**.021**	-0.12 (−0.34 to 0.09)	.269	-0.13 (−0.32 to 0.07)	.194	-0.83 (−1.51 to −0.15)	.018	0.08 (−0.21 to 0.37)	.586
Speaks language other than English														
Yes	-0.87 (−1.98 to 0.23)	.121	2.64 (−0.97 to 6.26)	.152	2.05 (0.06–4.05)	**.044**	0.91 (−0.12 to 1.94)	.082	0.57 (−0.36 to 1.49)	.228	8.82 (5.56–12.08)	< .001	-1.01 (−2.43 to 0.41)	.163
No	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Parental status														
Yes	-0.73 (−1.74 to 0.27)	.153	3.60 (0.31–6.89)	.032	3.32 (1.51–5.14)	**< .001**	0.73 (−0.21 to 1.67)	.126	0.19 (−0.65 to 1.04)	.657	-0.05 (−2.03 to 2.94)	.976	0.47 (−0.83 to 1.76)	.481
No	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
ECOG	0.10 (−0.63 to 0.82)	.792	1.30 (−1.05 to 3.65)	.278	0.73 (−0.57 to 2.02)	.272	0.29 (−0.39 to 0.96)	.402	1.40 (0.79–2.00)	**< .001**	0.88 (−1.26 to 3.02)	.420	-0.94 (−1.88 to −0.01)	**.048**
Self-efficacy	0.71 (0.03–1.39)	**.041**	-4.53 (−6.75 to −2.31)	**< .001**	-2.99 (−4.22 to −1.77)	**< .001**	-1.23 (−1.87 to −0.60)	**< .001**	-0.92 (−1.49 to −0.35)	**.002**	-2.24 (−4.26 to −0.22)	**.030**	1.51 (0.62–2.39)	**.001**
Attitude towards uncertainty	0.84 (0.00–1.67)	.05	2.66 (−0.07 to 5.39)	.056	1.77 (0.26–3.28)	**.021**	0.85 (0.07–1.63)	**.033**	0.70 (0.00–1.40)	.051	0.21 (−2.27 to 2.68)	.870	-0.40 (−1.49 to 0.69)	.474
Actionable results														
Yes	0.84 (0.04–1.64)	**.040**	-6.18 (−8.79 to −3.57)	**< .001**	-1.00 (−2.45 to 0.44)	.171	-0.16 (−0.91 to 0.59)	.669	0.13 (−0.54 to 0.81)	.696	-2.50 (−4.88 to −0.12)	**.039**	0.54 (−0.49 to 1.56)	.302
No	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	

Ref. = Reference category

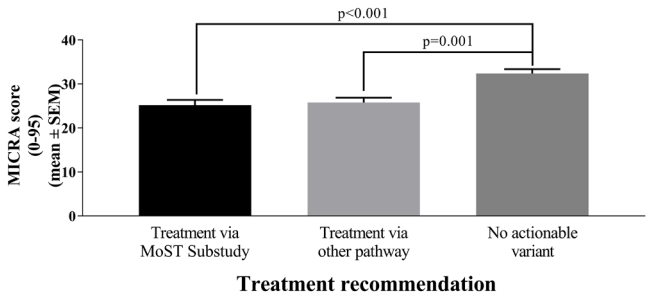

Fig. 2. MICRA scores by result of CTGP. Data represent average ± SEM.

3. Results

In this longitudinal study, 1525 participants were recruited to MoST between October 2016 and October 2019, of whom 1422 (93%) completed the T0 questionnaire. Of consented participants, 1191 received results (the remainder died or were waiting for results), of whom 560 (47%) completed the T1 questionnaire (see Fig. 1 for patient flow through the study).

Those who were female (p = 0.039), older (p = 0.03) with a first degree relative with cancer (p = 0.019), who spoke English at home (p > 0.001) and who received an actionable result and were offered ensured access to treatment via MoST (p = 0.004) were more likely to complete the T1 questionnaire, as were those with better ECOG status (p = 0.001), more negative attitudes towards uncertainty (p = 0.001), and higher self-efficacy (p = 0.002) at baseline. Some of these variables were significantly correlated with death since study entry (results available on request); thus it appears that overall, sicker and less empowered participants were less likely to complete T1.

Participants who completed the T1 questionnaire had a mean age of 56.34 years (range 18–89 years), with an even gender distribution (Table 2). Two hundred and forty (43%) had a university education and 56 (10%) lived in rural/remote areas of Australia. Actionable results were received by 356 (64%) participants, comprising 151 who were offered ensured access to treatment via a MoST substudy and 205 recommended treatment potentially accessible through their oncologist. A non-actionable variant result was received by 204 participants. At baseline, groups differed only on knowledge (F=3.22, p = 0.041). Patients with an actionable result recommended treatment potentially accessible through their oncologist had greater knowledge than those who received a non- actionable variant (t = 2.53, p = 0.035). Thus, we controlled for knowledge in all analyses comparing treatment groups.

3.1. Impact of receiving genetic test results

Psychological outcomes at T1 revealed significant distress, unsurprising in an advanced cancer population who had failed several treatment options (see Table 2). Cancer-specific anxiety (IES) was elevated, with proportions in the clinical range (≥8) ranging from 38% to 52% across groups. Mean general anxiety and depression scores were low, however 34–42% and 21–27% scored in the clinical range (≥8) for anxiety and depression symptoms respectively. Mean MICRA distress scores were low (6.08–8.19 across result groups), while uncertainty scores (means 13.82–15.60) were higher and comparable with those reported in other cancer populations [19]. Participants were on the whole very satisfied with their decision to have testing (mean of 25.34–26.54 out of a possible total of 30).

Consistent with *Hypothesis 1*, patients with actionable results reported lower levels of psychological distress and higher satisfaction with CTGP compared with those receiving non-actionable results (Table 3 and Fig. 2). Specifically, when controlling for gender, age, education, English-speaking, parental status, ECOG, baseline self-efficacy and attitude towards uncertainty, patients who received actionable results had MICRA scores on average 6.16 points lower than those without an actionable result ($p < 0.001$, 95% CI 8.79–3.57), IES scores 2.50 points lower ($p = 0.039$, 95% CI −4.88 to −0.12), and satisfaction scores 0.84 points higher ($p = 0.04$, 95% CI 0.04–1.64). Of note, 52% of those receiving a non-actionable result scored above the clinical range on the IES (cancer related anxiety), versus 41% and 38% of those with actionable results with and without a MoST study recommendation respectively. Other outcomes were not impacted by actionable versus non-actionable results.

In partial support of *Hypothesis 2,* availability of treatment was shown to modify the impact of receipt of actionable results. When controlling for demographics, knowledge, self-efficacy and attitude towards uncertainty, patients with actionable results offered ensured access to treatment within the MoST Program had HADS anxiety scores on average 1.45 points lower ($p = 0.002$, 95% CI −2.38 to −0.52), HADS depression scores 1.13 points lower ($p = 0.01$, 95% CI −1.98 to −0.27) and levels of hope 2.11 points higher ($p = .002$, 95% CI 0.81–3.40) than those recommended treatment potentially accessible via their oncologist. Of those with actionable results, 41% of those recommended treatment potentially accessible via their oncologist scored in the clinical range of anxiety on the HADS, versus 34% of those offered a MoST substudy (Table 4). Other outcomes were not impacted by treatment path.

Consistent with *Hypothesis 3*, both positive attitudes towards uncertainty and higher self-efficacy for coping with results impacted a number of outcomes. Patients with more positive attitudes towards uncertainty reported HADS anxiety scores on average 0.88 points lower ($p = 0.027$, 95% CI 0.10–1.65) and HADS depression scores on average 0.72 points lower ($p = 0.043$, 95% CI 0.02–1.42) than patients with more negative attitudes towards uncertainty (see Table 5). However, they reported MICRA uncertainty subscale scores on average 1.77 points higher $p = 0.021$, 95% CI 0.26–3.28). Patients with higher self-efficacy for coping with results reported MICRA total scores on average 4.56 points lower ($p < 0.001$, 95% CI −6.79 to −2.34) than patients with lower self-efficacy, as well as HADS anxiety scores 1.28 points lower ($p < 0.001$, 95% CI −1.91 to −0.64), HADS depression scores 0.95 points lower ($p = 0.001$, 95% CI −1.52 to −0.38), IES scores 2.29 points lower ($p = 0.027$, 95% CI −4.31 to −0.27), MICRA uncertainty 3 points lower ($p < 0.001$, 95% CI −4.23 to −1.77), hope (HHI) 1.54 points higher ($p = 0.001$, 95% CI 0.67–2.42) and satisfaction with the decision to have CTGP 0.73 points higher ($p = 0.037$, 95% CI 0.04–1.41). Interactions between self-efficacy and attitude to uncertainty with result type were non-significant.

Contrary to *Hypothesis 3*, patients with a higher knowledge of CTGP reported higher levels of HADS anxiety (on average 0.24 points) than patients with a lower knowledge of CTGP ($p = 0.034$, 95% CI 0.02–0.46). There were no other differences found regarding knowledge and other outcomes (Table 5), or interactions with result type.

3.2. Demographic/disease variables

Notably, several demographic and disease variables were associated with poorer psychosocial outcomes (Tables 3–5). Younger patients, parents, those with lower education, and who did not speak English at home, had poorer psychosocial outcomes after receipt of non-actionable results or receipt of actionable results but not recommended treatment within MoST. Notably, lower education and not speaking English at home were both significantly correlated with knowledge of CTGP (p = 0.001 and 0.002 respectively). Thus, knowledge may have mediated the impact of these variables on psychological outcomes.

4. Discussion and conclusion

4.1. Discussion

This study is one of the first to explore the impact of result return

Table 4
Summary of Significant Results from Linear Regression Analysis – Hypothesis 2: Availability of treatment: via MoST (n = 151) versus Other (n = 205.

	Satisfaction with Decision		MICRA TOTAL		MICRA_Uncertainty		HADS_Anxiety		HADS_Depression		Impact of Events		Hope Herth Index		Decisional Conflict	
Independent Variables	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**
Sex	-0.50 (−1.50 to 0.51)	.333	0.86 (−2.40 to 4.13)	.604	1.33 (−0.45 to 3.12)	.143	0.62 (−0.31 to 1.55)	.187	-0.31 (−1.17 to 0.54)	.471	-0.04 (−2.82 to 2.74)	.979	-0.20 (−1.46 to 1.06)	.755	-2.70 (−8.28 to 2.88)	.341
Age (for every 10-year increase)	-0.04 (−0.41 to 0.34)	.853	-0.60 (−1.82 to 0.61)	.328	-0.54 (−1.20 to 0.13)	.113	-0.57 (−0.92 to −0.22)	**.001**	-0.21 (−0.53 to 0.11)	.199	0.04 (−1.00 to 1.08)	.941	0.49 (0.02–0.96)	.043	-.25 (−1.76 to 0.23)	.808
Education	0.10 (−0.20 to 0.40)	.504	-0.58 (−1.55 to 0.38)	.235	-0.52 (−0.45 to 3.12)	.052	-0.12 (−0.39 to 0.16)	.408	-0.10 (−0.35 to 0.16)	.457	-0.41 (−1.24 to 0.41)	.327	0.04 (−0.32 to 0.40)	.821	0.04 (−1.64 to 1.71)	.965
Speaks language other than English																
Yes	-0.88 (−2.37 to 0.60)	.244	7.19 (2.36–12.03)	.004	4.05 (1.41–6.70)	**.003**	1.87 (0.50–3.24)	**.008**	1.46 (0.19–2.72)	**.024**	12.16 (8.05–16.28)	**< .001**	-2.72 (−4.57 to −0.88)	.004	3.89 (−4.57 to 12.35)	.366
No	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Parental status																
Yes	-0.84 (−2.08 to 0.41)	.186	3.12 (−0.91 to 7.14)	.128	3.20 (1.00–5.40)	**.004**	1.20 (0.06–2.35)	**.040**	0.30 (−0.76 to 1.35)	.584	0.44 (−3.00 to 3.88)	.801	0.39 (−1.14 to 1.92)	.616	4.39 (−2.74 to 11.51)	.227
No			Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
ECOG	-0.04 (−0.98 to 0.89)	.932	2.79 (−0.22 to 5.80)	.069	1.47 (−0.18 to 3.11)	.081	0.58 (−0.29 to 1.44)	.191	1.47 (0.67–2.27)	**< .001**	1.91 (−0.68 to 4.50)	.147	-1.27 (−2.44 to −0.11)	**.032**	4.34 (−0.79 to 9.46)	.097
Self-efficacy	0.35 (−0.55 to 1.24)	.446	-6.13 (−9.03 to −3.23)	**< .001**	-3.69 (−5.27 to −2.11)	**< .001**	-1.57 (−2.39 to −0.74)	**< .001**	-1.09 (−1.85 to −0.33)	**.005**	-2.13 (−4.60 to 0.35)	.092	1.67 (0.55–2.79)	**.004**	-7.41 (−12.15 to −2.66)	**.002**
Attitudes towards uncertainty	0.81 (−0.25 to 1.88)	.133	3.13 (−0.31 to 6.56)	.074	2.23 (0.35–4.10)	**.020**	0.85 (−0.13 to 1.83)	.089	0.84 (−0.06 to 1.74)	.068	-0.07 (−3.01 to 2.86)	.959	0.22 (−1.11 to 1.55)	.750	3.57 (−2.37 to 9.50)	.238
Available via MoST Substudy																
Yes	0.56 (−0.45 to 1.56)	.277	-1.34 (−4.60 to 1.93)	.422	-0.11 (−1.90 to 1.68)	.904	-1.45 (−2.38 to −0.52)	**.002**	-1.13 (−1.98 to −0.27)	**.010**	-1.92 (−4.70 to 0.86)	.175	2.11 (0.81–3.40)	**.002**	0.66 (−4.81 to 6.13)	.812
No	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	

Ref. = Reference category

Table 5
Summary of significant results from linear regression analysis - hypothesis 3: self-efficacy, attitudes to uncertainty and knowledge.

	Satisfaction with Decision		MICRA TOTAL		MICRA_Uncertainty		HADS_Anxiety		HADS_Depression		Impact of Events Scale		Hope	
Independent Variables	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**	**Regression Coefficient (95% CI)**	***p* value**
Sex	0.32 (−0.46 to 1.10)	.423	1.20 (−1.38 to 0.13)	.356	-1.37 (−2.78 to 0.04)	.056	-0.65 (−1.37 to 0.08)	.080	0.39 (−0.26 to 1.04)	.243	-0.47 (−2.79 to 1.84)	.689	-0.24 (−1.25 to 0.77)	.640
Age (for every 10-year increase)	-0.01 (−0.31 to 0.30)	.960	-1.14 (−2.14 to −0.15)	**.024**	-0.73 (−1.28 to −0.18)	**.009**	-0.58 (−0.86 to −0.30)	**< .001**	-0.26 (−0.51 to 0.00)	**.048**	-0.27 (−1.17 to 0.64)	.562	0.50 (0.11–0.89)	**.012**
Education	0.08 (−0.15 to 0.32)	.479	-0.63 (−1.38 to 0.13)	.102	-0.49 (−0.91 to −0.08)	**.021**	-0.12 (−0.33 to 0.09)	.271	-0.13 (−0.32 to 0.07)	.196	-0.82 (−1.51 to −0.14)	**.018**	0.07 (−0.22 to 0.36)	.624
Speaks language other than English														
Yes	0.90 (−0.21 to 2.01)	.110	2.68 (−0.93 to 6.30)	.145	-2.05 (0.06–4.05)	**.044**	-0.98 (−2.00 to 0.04)	.060	-0.62 (−1.54 to 0.30)	.186	8.90 (5.64–12.16)	**< .001**	1.11 (−0.31 to 2.52)	.124
No	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Parental status														
Yes	0.77 (−0.24 to 1.78)	.133	3.67 (0.37–6.97)	**.029**	3.33 (1.50–5.15)	**< .001**	-0.83 (−1.76to 0.11)	.083	-0.27 (−1.11 to 0.58)	.537	-0.08 (−3.07 to 2.91)	.959	-0.34 (−1.63 (0.95)	.603
No			Ref.		Ref.									
ECOG	0.09 (−0.63 to 0.82)	.799	1.31 (−1.04 to 3.67)	.273	0.73 (−0.57 to 2.03)	.273	0.30 (−0.37 to 0.97)	.381	1.40 (0.80–2.01)	**< .001**	0.89 (−1.25 to 3.03)	.414	-0.94 (−1.87 to −0.02)	**.046**
Self-efficacy	0.73 (0.04–1.41)	**.037**	-4.56 (−6.79 to −2.34)	**< .001**	-3.00 (−4.23 to −1.77)	**< .001**	-1.28 (−1.91 to −0.64)	**< .001**	-0.95 (−1.52 to −0.38)	**.001**	-2.29 (−4.31 to −0.27)	**.027**	1.54 (0.67–2.42)	**.001**
Attitudes towards uncertainty	0.83 (−0.01 to 1.67)	.052	2.69 (−0.04 to 5.41)	.054	1.77 (0.26–3.28)	**.021**	0.88 (0.10–1.65)	**.027**	0.72 (0.02–1.42)	**.043**	0.24 (02.23–2.71)	.849	-0.41 (−1.49 to 0.67)	.459
Knowledge†	-0.02 (−0.26 to 0.22)	.879	-0.23 (−1.00 to 0.53)	.546	-0.16 (−0.58 to 0.26)	.460	0.24 (0.02–0.46)	**.034**	0.18 (−0.01 to 0.04)	.062	0.15 (−0.56 to 0.86)	.678	-0.18 (−0.47 to 0.12)	.237
Treatment recommendation														
Treatment via MoST substudy	1.17 (0.20–2.15)	**.019**	-6.90 (−10.11 to −3.69)	**< .001**	-1.04 (−2.81 to 0.73)	.250	-0.96 (−1.87 to −0.05)	**.038**	-0.50 (−1.31 to 0.32)	.234	-3.55 (−6.44 to −0.65)	**.016**	1.85 (0.53–3.18)	**.006**
Treatment via 'other'	0.59 (−0.32 to 1.49)	.201	-5.66 (−8.60 to −2.72)	**< .001**	-0.98 (−2.60 to 0.64)	.237	0.43 (−0.41 to 1.27)	.313	0.60 (−0.15 to 1.36)	.117	-1.71 (−4.39 to 0.97)	.210	-0.19 (−1.31 to 0.93)	.742
Non-actionable variant	Ref.		Ref.		Ref.		Ref.				Ref.		Ref.	

Ref. = Reference category
†Knowledge was added to the model in a separate analysis using a subset of participants who completed this measure (N = 443)

after CTGP on the psychological well-being of patients with advanced, incurable cancer receiving or having failed their last line of therapy. This population is facing loss of hope and impending death. Thus, for many, CTGP offers a last opportunity to find a tailored treatment which would offer them more time or (perceived) potential cure [24]. Given the vulnerability of this patient group, it is critical that we attend to the psychosocial impact when CTGP fails to meet expectations.

As predicted, patients receiving non-actionable results reported greater result-specific distress, higher cancer-specific anxiety and less satisfaction with their decision to have CTGP, than those receiving actionable results. Patients with advanced cancer are known to have unrealistic expectations for chemotherapy, [25] and this is likely true of genomic testing as well. When these hopes are dashed, patients can experience significant distress and reduced satisfaction with testing decisions. Over half of those with non-actionable results were in the clinical range for cancer-specific anxiety, suggesting that receipt of non-actionable results should prompt exploration of need for counseling and support, as suggested by others [26]. Palliative care referral has also been found helpful in this scenario [27].

Participants receiving a non-actionable result did not, however, experience greater uncertainty, general depression or anxiety, or less hope, than those receiving actionable results. This may reflect the high level of uncertainty inherent to cancer, [28] and accompanying even actionable results, which might precipitate experimental treatments of unknown benefit where prolongation of life, rather than cure, is the goal of therapy.

For those receiving an actionable result, only a few variables were associated with the treatment pathway. Thus hypothesis 2 was partially supported. Those offered treatment through MoST reported less general anxiety and depression and higher hope than those advised to consult their oncologist about treatment. Indeed, 7% more patients recommended treatment through their oncologist experienced anxiety symptoms in the clinical range, than those recommended a MoST substudy. This difference may be due to challenges experienced by oncologists in accessing recommended drugs, while the treatments offered via MoST itself are by definition available. In addition, drug access outside of trials may entail out-of-pocket expenses. Notably, more patients recommended treatment through MoST completed the T1 questionnaire than other result groups, suggesting this group was also more engaged with and positive about the research. However, treatment offered did not impact participants' satisfaction with their decision to undergo CTGP, or other outcomes.

In line with Uncertainty in Illness Theory, [9] those with more negative attitudes towards uncertainty experienced higher general anxiety and depression, regardless of the result they received. Similarly, as predicted by Social Cognitive Theory, [13] lower self-efficacy to cope with results was strongly associated with negative outcomes. Both these variables may be useful targets for pre-test screening to identify those likely most vulnerable to negative psychosocial outcomes, regardless of result return. Targeting interventions to this sub-group may minimize negative psychosocial sequalae and allow more cost-effective provision of psychosocial care.

We found knowledge of CTGP and its implications was associated with increased, rather than decreased anxiety, however the differences in anxiety were small. Patients who had invested the time to research and understand the test may be more invested and anxious about its outcome, whereas those with lower knowledge might have less of an understanding about their likelihood of accessing personalized treatment. Another study of patients with metastatic breast cancer undergoing testing to guide treatment earlier in their cancer trajectory, found that knowledge did not impact psychological outcomes [29]. Simply presenting more or better information to ensure patients have realistic expectations prior to result return, may not prevent disappointment or mitigate the effect of receiving non-actionable findings. Further, in the study above, [29] education level was not associated with genetic knowledge. Thus, predicting who will need more information to address health illiteracy is not straightforward. The impact of knowledge needs further exploration in future studies.

The finding that younger participants and those with children had poorer psychosocial outcomes is consistent with the literature. Younger age has been found to predict greater distress in a variety of cancer populations, [30] perhaps reflecting life stage as well as a greater existential crisis concerning an unexpected, shortened lifespan. Similarly, many studies have reported that low education and migrant status predict poorer cancer psychosocial outcomes, [31,32] possibly due to poorer access to support. As we found a correlation between these variables and knowledge of CTGP, it is also possible that low health literacy impacted their psychological outcomes.

A number of limitations impact the results of this study. Participants received CTGP in the context of a research study and this may not fully reflect the experience of patients offered CTGP in routine care. Our sample included a higher proportion of university-educated participants than in the general public, possibly reflecting those likely to consent to research participation. Fifty percent of the sample did not complete the T1 questionnaire. Our analyses suggested that poor health was likely to account for much of this dropout, but the potential for bias remains, thus results may not generalize to patients with lower education or worse health. Our participants appeared more empowered and active on outcome measures, suggesting that outcomes may have been worse if the whole sample had been included. We measured psychological impacts immediately post result receipt; future research should explore longer term impacts. Note, testing for germline mutations while planned, had not occurred at the time this analysis was conducted, and so we are unable to report on those. Study strengths included the essentially random nature of result received, allowing causal, rather than associative relationships to be inferred.

5. Conclusion

In summary, this longitudinal study investigating the outcomes of receiving CTGP results in advanced cancer patients has demonstrated poorer psychosocial outcomes in a subset of those receiving non-actionable results, as well as in those not offered an ensured treatment option.

5.1. Practice implications

Since negative attitudes towards uncertainty and low self-efficacy to cope with results at baseline predicted poorer outcomes regardless of result type, these variables offer a potential screening target that may identify vulnerable individuals who may benefit from proactive support. Similarly, it appears that people with low education and who do not speak English at home are a vulnerable population who might benefit from greater support. Assessment of individuals who do not receive actionable results with ensured access to tailored treatment may identify a subset who could benefit from counseling at this time.

CRediT authorship contribution statement

Phyllis Butow: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing, **Megan Best**: Conceptualization, Funding acquisition, Methodology, Writing – review & editing, **Grace Davies**: Formal analysis, Writing – review & editing, **Timothy Schlub**: Formal analysis, Methodology, Writing – review & editing, **Christine Napier**: Data curation, Methodology, Writing – original draft, Writing – review & editing, **Nicci Bartley**: Project administration, Writing – review & editing, **Mandy Ballinger**: Conceptualization, Funding acquisition, Resources, Writing – review & editing, **Ilona Juraskova**: Conceptualization, Methodology, Writing – review & editing, **Bettina Meiser**: Conceptualization, Methodology, Writing – review & editing, **Barbara B Biesecker**: Conceptualization, Writing – review & editing, **David Thomas**:

Conceptualization, Funding acquisition, Resources, Writing – review & editing.

Declaration of competing interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

We thank the patients who participated in the PiGeOn Project. We also thank Ainsley Newson, Katherine Tucker, Chris Jacobs, Jacqueline Savard, Mary-Anne Young, Judy Kirk, Kate Vines, and Richard Vines for their contributions to this study.

This study was funded by a National Health and Medical Research Council (NHMRC) of Australia Project Grant (ID1124749). MCB is funded by a Post-Doctoral Research Fellowship from the Cancer Institute of New South Wales (MB00352). PB is funded by an NHMRC Senior Principal Research Fellowship (APP1121630). BM holds a NHMRC Senior Research Fellowship, Level B (ID1078523). MLB is supported by a Cancer Institute of NSW Career Development Fellowship (CDF171109). DMT is funded by an NHMRC Principal Research Fellowship (APP1104364).

I confirm all patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified through the details of the story.

References

[1] Jackson SE, Chester JD. Personalised cancer medicine. Int J Cancer 2015;37(2):262–6.
[2] Mandelker D, Zhang L, Kemel Y, Stadler ZK, Joseph V, Zehir A, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 2017;318(9):825–35.
[3] Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL. Molecular profiling for precision cancer therapies. Genome Med 2020;12(8):8. https://doi.org/10.1186/s13073-019-0703-1.
[4] Williams JL, Rahm AK, Zallen DT, Stuckey H, Fultz K, Fan AL, et al. Impact of a patient-facing enhanced genomic results report to improve understanding, engagement, and communication. J Genet Couns 2018;27:358–69. https://doi.org/10.1007/s10897-017-0176-6.
[5] Liang R, Meiser B, Smith S, Kasparian NA, Lewis CR, Chin M, et al. Advanced cancer patients' attitudes towards, and experiences with, screening for somatic mutations in tumours: a qualitative study. Eur J Cancer Care 2017;26(6). https://doi.org/10.1111/ecc.12600.
[6] Yanes T, Willis AM, Meiser B, Tucker KM, Best M. Psychosocial and behavioral outcomes of genomic testing in cancer: a systematic review. Eur J Hum Genet 2018;27(1):28–35. https://doi.org/10.1038/s41431-018-0257-5.
[7] Marron JM, DuBois SG, Glade Bender J, Kim A, Crompton BD, Meyer SC, et al. Patient/parent perspectives on genomic tumour profiling of pediatric solid tumors: the individualized cancer therapy (iCat) experience. Pedia Blood Cancer 1982;63(11):1974–82. https://doi.org/10.1002/pbc.26137.
[8] Biesecker BB, Klein W, Lewis KL, Fisher TC, Wright MF, Biesecker LG, et al. How do research participants perceive "uncertainty" in genome sequencing? Genet Med 2014;16(12):977–80.
[9] Mishel M. Reconceptualization of the uncertainty in illness theory. J Nurs Scholarsh 1990;22(4):256–62.
[10] Newson AJ, Leonard SJ, Hall A, Gaff CL. Known unknowns: building an ethics of uncertainty into genomic medicine. BMC Med Genom 2016;9:57. https://doi.org/10.1186/s12920-016-0219-0.
[11] Han PK, Klein WM, Arora NK. Varieties of uncertainty in health care: a conceptual taxonomy. Med Decis Mak 2011;31(6):828–38.
[12] Babrow AS, Kline KN. From "reducing" to "coping with" uncertainty: reconceptualizing the central challenge in breast self-exams. Soc Sci Med 2000;51(12):1805–16.
[13] Bandura A. Social cognitive theory: an agentic perspective. Asian J Soc Psychol 1999;2:21–41. https://doi.org/10.1111/1467-839X.00024.
[14] Chirico A, Lucidi F, Merluzzi T, Alivernini F, Laurentiis M, Botti G, et al. A meta-analytic review of the relationship of cancer coping self-efficacy with distress and quality of life. Oncotarget 2017;8(22):36800–11.
[15] Thavaneswaran S, Sebastian L, Ballinger M, Best M, Hess D, Lee CK, et al. Cancer molecular screening and therapeutics (MoST): a framework for multiple, parallel, signal-seeking studies of targeted thearpies for rare and neglected cancers. Med J Aust 2018;209(8):354–5. https://doi.org/10.5694/mja18.00227.
[16] Best M, Newson AJ, Meiser B, Juraskova I, Goldstein D, Tucker K, et al. The PiGeOn project: protocol for a longitudinal study examining psychosocial, behavioural and ethical issues and outcomes in cancer tumour genomic profiling. BMC Cancer 2018;18(1):389.
[17] Rosenberg SM, Tracy MS, Meyer ME, Sepucha K, Gelber S, Hirshfield-Bartek J, et al. Perceptions, knowledge, and satisfaction with contralateral prophylactic mastectomy among young women with breast cancer: a cross-sectional survey. Ann Intern Med 2013;159(6):373–81.
[18] Braithwaite D, Sutton S, Steggles N. Intention to participate in predictive genetic testing for hereditary cancer: the role of attitude toward uncertainty. Psychol Health 2002;17:761–72.
[19] 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.
[20] Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med 1979;41(3):209–18.
[21] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361–70.
[22] Holmes-Rovner M, Kroll J, Schmitt N, Rovner DR, Breer ML, Rothert ML, et al. Patient satisfaction with health care decisions the satisfaction with decision scale. Med Decis Mak 1996;16(1):58–64.
[23] Herth K. Abbreviated instrument to measure hope: development and psychometric evaluation. J Adv Nurs 1992;17(10):1251–9. https://doi.org/10.1111/j.1365-2648.1992.tb01843.x.
[24] Best MC, Bartley N, Jacobs C, Juraskova I, Goldstein D, Newson AJ, et al. Patient perspectives on molecular tumor profiling: "Why wouldn't you?". BMC Cancer 2019;19:753. https://doi.org/10.1186/s12885-019-5920-x.
[25] Weeks JC, Catalano PJ, Cronin A, Finkelman MD, Mack JW, Keating NL, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med 2012;367(17):1616–25.
[26] McBride CM, Guan Y, Hay JL. Regarding the Yin and Yang of precision cancer-screening and treatment: are we creating a neglected majority? Int J Environ Res Public Health 2019;16(21):4168.
[27] Temel JS, Gainor JF, Sullivan RJ, Greer JA. Keeping expectations in check with immune checkpoint inhibitors. J Clin Oncol 2018;36(17):1654–7.
[28] Hall DL, Mishel MH, Germino BB. Living with cancer-related uncertainty: associations with fatigue, insomnia, and affect in younger breast cancer survivors. Support Care Cancer 2014;22(9):2489–95.
[29] Adams EJ, Asad S, Reinbolt R, Collier KA, Abdel-Rasoul M, Gillespie S, et al. Metastatic breast cancer patient perceptions of somatic tumor genomic testing. BMC Cancer 2020;20(1):389. https://doi.org/10.1186/s12885-020-06905-2.
[30] Hamilton J, Kruse H, Holcomb L, Freche R. Distress and psychosocial needs: demographic predictors of clinical distress after a diagnosis of cancer. Can J Oncol Nurs 2018;22(4):390–7.
[31] Smith AB, Butow P, Olver I, Luckett T, Grimison P, Toner G, et al. A systematic review of quantitative observational studies investigating psychological distress in testicular cancer survivors. Psycho-Oncology 2018;27(4):1129–37.
[32] Luckett T, Goldstein D, Butow P, Gebski V, Aldridge LJ, McGrane J, et al. Psychological morbidity and quality of life of ethnic minority patients with cancer: a systematic review and meta-analysis. Lancet Oncol 2011;12(13):1240–8. https://doi.org/10.1016/S1470-2045(11)70212-1.