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ORIGINAL ARTICLE

Longitudinal patterns in fear of cancer progression in patients with rare, advanced cancers undergoing comprehensive tumour genomic profiling

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Abstract

Introduction: Fear of cancer progression (FCP) impacts quality of life and is a prevalent unmet need in patients diagnosed with advanced cancer, particularly as treatment options are reduced. We aimed to identify longitudinal patterns in FCP over 6 months in patients with advanced cancer receiving comprehensive tumour genomic profiling (CTGP) results, and their correlates.

Methods: Patients with pathologically confirmed metastatic disease (~70% rare cancers) receiving or post their last line of standard therapy completed questionnaires at T0 (prior to CTGP), T1 (immediately post CTGP results) and T2 (2 months later).

Results: High stable ($N = 52$; 7.3%) and low/moderate stable ($N = 56$; 7.8%) FCP patterns over time typified the largest participant groups ($N = 721$). Those with an immediately actionable variant versus a non-actionable variant ($p = 0.045$), with higher FCP ($p < 0.001$), and lower Functional Assessment of Chronic Illness Therapy—Spiritual Well-being (FACIT-Sp) scores ($p = 0.006$) at T0, had higher FCP at T1. Those with higher FCP at T0 ($p < 0.001$) and at T1 ($p < 0.001$), lower FACIT-Sp

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scores at T1 ($p = 0.001$), lower education ($p = 0.031$) and female gender ($p = 0.027$) had higher FCP at T2.

Discussion: Routine screening for psychological/spiritual characteristics in those about to undergo CTGP may help to identify patients who may benefit from closer monitoring and provision of psychosocial support. Future studies should explore interventions to best address FCP in this vulnerable group, as interventions assessed to date have almost all addressed patients with curative cancers or newly diagnosed advanced disease.

KEYWORDS
advanced cancer, cancer, comprehensive tumour genomic profiling, fear of cancer progression, genomics, longitudinal, oncology, Psycho-oncology, psychosocial

1 | BACKGROUND

Fear of cancer recurrence (FCR) or progression (FCP), defined as 'fear, worry or concern relating to the possibility that cancer will come back or progress',[1] is a common and distressing concern after a cancer diagnosis, for which patients often seek help.[2] As is clear from the definition above (which includes both constructs), FCR and FCP share many characteristics, and are therefore often treated as a single construct. Nevertheless, the literature has primarily focused on FCR in curatively treated cancers. FCP in the context of advanced cancer is poorly understood.

FCP is closely associated with existential distress.[3] Patients with high FCP experience frequent intrusive thoughts about cancer that are difficult to control, believe strongly that the cancer will progress, describe more elaborate death-related thoughts and feel alone in their experience.[4–6] These responses are consistent with Terror Management Theory,[7] which argues that a core driver of many human emotions and behaviour is the fear of death or annihilation, and suggests that humans develop a series of defences, including denial and a search for meaning or transcendence, to guard against these fears. Several recent conceptualisations of FCR have suggested a critical role for death anxiety.[3,8,9]

High FCR/P negatively impacts emotions, relationships, work, goal setting and quality of life,[10–12] and increases healthcare costs.[11] It is important to understand the prevalence, causes and patterns of FCP over time, so that those at risk can be identified early, and given appropriate services.

Data on the prevalence and stability of FCP can be deduced primarily from studies of mixed samples which do not report data separately for those with advanced cancer. Of 118 women with gynaecological cancers of mixed stages,[13] 50% had high FCR/P persisting over time. Similarly, between 44% and 56% of 962 cancer survivors, of whom 200 had metastatic disease, reported high FCP, with most remaining at that level over the 18-month follow-up.[14] Diverse factors have been associated with FCR/P, including younger age and female gender,[15] anxiety, depression, stress symptoms[16] and intrusive thinking, death anxiety, threat appraisal and meta-cognitions.[3]

Longitudinal studies[17–24] have not, to date, examined FCP over time in patients with rare cancers receiving comprehensive tumour genomic profiling (CTGP), where patients may experience uncertainty as they wait for results, or receive results which dash hope for personalised treatments after standard treatments have failed. Even if positive results are obtained, uncertainty regarding long-term outcomes from relatively new treatments may maintain high FCP.

We aimed to identify FCP patterns over 6 months in patients with advanced, primarily rare cancers undergoing CTGP, and their correlates. The study was guided by Social Cognitive Theory,[25] which suggests that high confidence in ability to cope (high perceived self-efficacy) predicts less distress under stressful conditions. This theory was supported by a recent meta-analysis of 108 studies showing a strong negative relationship between perceived self-efficacy and distress in cancer patients.[26] A negative attitude to illness uncertainty (inability to determine the meaning or outcome of illness-related events)[27] has also been associated with psychological outcomes such as excessive worrying[28] and reassurance-seeking,[29] both features of FCP. On the basis of these theories, and Terror Management Theory, we hypothesised that:

1. The majority of patients (>50%) will have high FCP (scores above the median) at baseline, which will remain stable after CTGP result receipt (T1) and at follow-up 2–3 months later (T2), as found in previous longitudinal studies of FCR/P.
2. FCP will be higher (scores above the median) after CTGP result receipt (T1), which will remain stable at follow-up (T2) in participants who receive non-actionable CTGP results compared to those who receive actionable results.
3. Socio-demographic factors (female gender and younger age) and psychological factors (low self-efficacy, negative attitude to uncertainty, high perceived susceptibility to cancer progression and low spiritual well-being) will be related to high FCP (scores above the median) at baseline (T0), which will remain stable at T1 and

T2, as predicted by social cognitive, uncertainty and existential distress theories, and previous studies.

4. Cognitive factors (poor knowledge) will be related to high FCP (scores above the median) at baseline (T0), which will remain stable at T1 and T2, as FCP can lead to avoidance,[7] including of information.

2 | METHODS

2.1 | Participants and study design

Participants were recruited from the Molecular Screening and Therapeutics (MoST) study[30] from 2016 to 2019. The MoST study recruits adults with pathologically confirmed metastatic solid cancers (70% have rare cancers), receiving or post their last line of standard therapy, via their oncologists. Eligibility criteria include an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–3 and sufficient accessible tissue for CTGP. Participants undergo CTGP; results are reviewed by a Molecular Tumour Board. A CTGP report linking molecular targets with potential therapeutics is issued approximately 11 weeks post-consent. Actionable results include molecular targets for which treatment is available, either through a MoST clinical trial or another route. Non-actionable results include those without linked treatment recommendations.

The Psychosocial Issues in Genomics Oncology (PiGeOn) Project was a longitudinal, mixed methods psychosocial sub-study of the MoST study.[31] Participants completed questionnaires (paper-and-pen or online) at baseline prior to testing (T0), 1–4 weeks after receiving CTGP results (T1), and 2 months later (T2). A subset completed interviews at these time points also (data reported elsewhere).[32] The current paper reports longitudinal quantitative results related to FCP.

Human ethics approval was obtained from Human Research Ethics Committees at St Vincent's Hospital, Sydney, Australia (HREC/16/SVH/23).

2.2 | Measures

We used psychometrically validated scales where available and study-developed questions if published scales were inappropriate for our cohort.

At baseline (T0), the following measures were assessed:

Demographics/cancer variables: including gender, age, education, occupation, language spoken at home, postcode to determine socio-economic status and remoteness (using the Accessibility and Remoteness Index of Australia [ARIA]), marital and parental status, family history of cancer, multiple primary cancers diagnosis, time since cancer diagnosis and cancer incidence (per 100,000 population per year: >6 cases - common, 6-12 cases - less common or <6 cases - rare).

FCP: The three-item Concerns about Recurrence Questionnaire (CARQ),[33] adapted to measure FCP, for example, 'How emotionally upset or distressed have you been about your cancer progressing?'. Scores range from 0 to 30; higher scores indicate greater FCP.

Attitudes towards Uncertainty (in CTGP): Higher scores on this seven-item scale[34] (mean score possible range = 1–5) reflect a negative attitude towards uncertainty.

Perceived susceptibility (to cancer progression): One question used a visual analogue scale ranging from 0% to 100%.[35]

Self-efficacy (in coping with CTGP outcomes): Study-adapted questions based on Rosenberg et al.[36] rated on a 5-point Likert scale; high scores indicated greater self-efficacy (range 1–5).

Knowledge of genomics: Eight study-developed questions (Data S1) assessed, for example, purposes of CTGP and its ability to predict cancer risk and guide treatment. Percent of correct responses was calculated (score 0%–100%).

Spiritual well-being: The Functional Assessment of Chronic Illness Therapy—Spiritual Well-being (FACIT-Sp-12)[37] is comprised of three subscales: peace, meaning and faith. Scores range from 0 to 48; higher scores indicate greater spiritual well-being.

2.3 | CTGP result type

The CTGP result received was classified as: Non-actionable, Actionable: Recommended treatment via MoST sub-study, or Actionable: Recommended treatment via another pathway.

Immediately post result receipt (T1), and two months later (T2) participants completed the CARQ, FACIT-Sp-12 and Perceived susceptibility scales again.

2.4 | Statistical analyses

A preliminary analysis using Growth Mixture Modelling (GMM) following the approach of Ram and Grimm[38] was carried out. GMM is a data-driven approach aimed at identifying (rather than assuming) unobserved sub-populations (here differing in their FCP) and their development over time. A number of linear and latent models with increasing numbers of sub-populations were fitted. A two-class (two sub-population) linear model was selected based on fit statics and because, when more sub-populations were included, estimation or convergence issues arose. The two sub-populations were both characterized as stable over time—just with different mean levels of FCP. See Data S2 for more detailed information on the analyses and results. Importantly, this analysis assumed a continuous time scale, whereas as the CTGP results were received prior to T1 and the time difference between assessment points differed slightly across individuals, a continuous time scale may not capture the event of receiving CTGP results with good precision. Therefore, to further investigate the impact that results receipt has on FCP, we additionally show all categorizations of outcomes and use regression to

identify predictors of FCP at T1 (shortly after receipt of CTGP outcomes) and T2 (long after results receipt).

As the CARQ lacks published cut-off scores in an advanced cancer population, a median split on FCP (FCP0 = 18) was applied to categorize participants as having high (≥18) versus low/moderate (<18) FCP at baseline. Change in FCP between T0 and T1 and between T1 and T2 was calculated. FCP change scores of half a standard deviation ($0.5 \times SD_{FCP0} = 4$) were classified as clinically significant increases or decreases. Change scores falling in between −4 and +4 were defined as stable FCP.

To test whether change in FCP over time is dependent on result type, FCP patterns were split into two time periods: T0–T1 (pre to post-result receipt), and T1–T2 (immediate to longer-term post-result receipt) and collapsed into four clinically meaningful patterns. These consisted of (1) initially high and either stable or increasing; (2) initially high and decreasing; (3) initially low and either stable or decreasing and (4) initially low and increasing. Chi-square tests were applied to test the dependency between result type and the patterns (Table S1).

Two multiple linear regressions were performed to predict (1) FCP at T1 and (2) FCP at T2 while controlling for FCP values at the previous time point(s). Demographics (e.g., age, sex), clinical variables (i.e., cancer incidence, having a first degree relative with cancer), CTGP result type, four psychosocial variables (i.e., uncertainty, spiritual well-being, self-efficacy and perceived susceptibility) and knowledge were entered simultaneously as predictors into the models. In the first model with FCP at T1 as dependent variable, psychosocial variables as assessed at T0 were entered as predictors. In the second model, psychosocial variables as assessed at T1 were entered as independent variables and for those not assessed at T1, the value at T0 was used. All analyses were performed in SPSS, version 25.

3 | RESULTS

Data of 721 participants were available: 373 had complete FCP data. Four, 162 and 182 had missing FCP values at T0 (baseline), T1 and T2, respectively. We compared patients with versus without missing FCP values on study variables. Patients with a missing value on FCP had significantly higher FCP at the second assessment ($M = 17.95$, SD = 8.3 vs. $M = 16.0$ SD = 8.1, $t[557] = -2.65$, $p = 0.008$), lower uncertainty at baseline ($M = 4.30$, SD = 0.56 vs. $M = 4.42$, SD = 0.53, $t[713] = 2.825$, $p = 0.005$) and differed in their ECOG value (52% of missing had an ECOG score of 0 vs. 62% of non-missing). Thus, those with missing values appeared to have somewhat worse functional status and higher FCP after result receipt than those with complete data (Figure S1 and Table S2).

Participants were mostly female (54.4%), middle-aged (56 years on average) and were first diagnosed >4 years ago (Table 1). Average FCP scores were in the mid-range (15.4–16.8 over time) with the full range of possible scores represented in the data (0–30). Half of participants ($N = 362$, 50.5%) initially had high FCR scores (≥18), similar to levels reported in earlier studies.[10,11]

TABLE 1 Sample descriptives

	Result types			
	Non-actionable	Actionable: Tx via MoST sub-study	Actionable: Tx via another pathway	Total
Demographic characteristics				
Age, years (mean, SD, range)	55 (14)	56 (14)	57 (14)	56 (14)
	18–89	20–84	21–88	18–89
Sex, female	154 (57)	104 (53.9)	134 (51.9)	392 (54.4)
Marital status, married	213 (78.9)	144 (74.6)	207 (80.2)	564 (78.2)
Education				
Secondary school or less	106 (39.3)	75 (38.9)	87 (33.7)	268 (37.2)
Vocational training	57 (21.1)	29 (15)	47 (18.2)	133 (18.4)
Undergraduate university	65 (24.1)	62 (32.1)	65 (25.2)	192 (26.6)
Postgraduate university	41 (15.2)	24 (12.4)	56 (21.7)	121 (16.8)
Missing	1 (0.4)	3 (1.6)	3 (1.2)	7 (1)
Medical/science occupation, no	247 (91.5)	181 (93.8)	235 (91.1)	663 (92)
Having children, yes	217 (80.4)	151 (78.2)	197 (76.4)	565 (78.4)

TABLE 1 (Continued)

	Result types			
	Non-actionable	Actionable: Tx via MoST sub-study	Actionable: Tx via another pathway	Total
Speaking English at home, yes	222 (82.2)	164 (85)	216 (83.7)	602 (83.5)
Accessibility and remoteness index of Australia				
Major city	189 (70)	136 (70.5)	181 (70.2)	506 (70.2)
Inner regional	54 (20)	39 (20.2)	45 (17.4)	138 (19.1)
Outer regional	26 (9.6)	14 (7.3)	26 (10.1)	66 (9.2)
Remote	1 (0.4)	3 (1.6)	6 (2.3)	10 (1.4)
Unknown/overseas	0	1 (0.5)	0	1 (0.1)
Clinical characteristics				
Eastern cooperative oncology group performance status				
0	150 (55.6)	108 (56)	151 (58.5)	409 (56.7)
1	109 (40.4)	78 (40.4)	100 (38.8)	287 (39.8)
2	10 (3.7)	5 (2.6)	4 (1.6)	19 (2.6)
Missing	1 (0.4)	2 (1.0)	3 (1.2)	6 (0.8)
Incidence				
Common (>6/100,000)	41 (15.2)	32 (16.6)	59 (22.9)	132 (18.3)
Less common (6-12/100,000)	21 (7.8)	22 (11.4)	34 (13.2)	77 (10.7)
Rare (<6/100,000)	208 (77)	139 (72)	165 (64)	512 (71)
Multiple primary cancers, no	238 (88.1)	156 (80.8)	216 (83.7)	610 (84.6)
Time since first cancer diagnosis, months (mean, SD, range)	47.7 (68) 0-412	53.6 (76) 0.4-483	54.4 (75) 0-504	51.7 (73) 0-504
First degree relative with cancer, yes	146 (54.1)	85 (44)	148 (57.4)	379 (52.6)
Fear of cancer progression (FCP)				
FCP0 (mean, SD, range)	17.3 (7.7) 0-30	16.4 (7.9) 0-30	16.7 (8.4) 0-30	16.8 (8) 0-30
FCP1 (mean, SD, range)	18.2 (7.8) 0.5-30	15.2 (8.3) 0-30	16.2 (8.3) 0-30	16.7 (8.2) 0-30
FCP2 (mean, SD, range)	16 (8.1) 0-30	14.4 (7.9) 0-30	15.6 (8.5) 0-30	15.4 (8.2) 0-30
Total	**270**	**193**	**258**	**721**

Note: Unless otherwise indicated, values represent patient numbers (*N*) and percentages.

Abbreviations: FCP, fear of cancer progression; SD, standard deviation; Tx, treatment.

Hypothesis 1: A substantial proportion of patients will have high FCP maintained over time.

GMM—which identifies sub-population trends with time—identified two sub-populations with stable FCP over time, one with an initial mean FCP of 18.6 and the other 4.83 (Data S2). Although further sub-populations were not statistically identified we show the number of occurrences of all possible changes to FCP with time in Table 2 to fully describe the entire population. In agreement with the GMM, high-stable ($N = 52$; 7.3%) and low/moderate-stable ($N = 56$; 7.8%) FCP patterns included the largest groups of participants. Thus Hypothesis 1 was partially supported.

Hypothesis 2: FCP will be higher and more sustained at T1 and T2 in participants who receive non-actionable CTGP results.

We found that result type was not associated with FCP changes across time (Table 2). To identify predictors of FCP, we therefore carried out multiple linear regression of FCP at T1 (shortly after receipt of results, Table 3) and T2 (long after receipt of results, Figure S1 and Table S2). The multiple

TABLE 2 Patterns of fear of cancer progression

	Result types			
	Non-actionable	Actionable: Tx via MoST sub-study	Actionable: Tx via another pathway	Total
High at baseline, *N* = 362 (50.5%)[a]				
Stable	20 (7.4)	17 (8.8)	15 (5.9)	52 (7.3)
Stable–increase	4 (1.5)	1 (0.5)	3 (1.2)	8 (1.1)
Stable–decrease	7 (2.6)	6 (3.1)	10 (3.9)	23 (3.2)
Decrease–stable	9 (3.3)	10 (5.2)	6 (2.4)	25 (3.5)
Decrease–increase	9 (3.3)	7 (3.6)	8 (3.1)	24 (3.3)
Decrease–decrease	5 (1.9)	4 (2.1)	9 (3.5)	18 (2.5)
Increase–stable	5 (1.9)	1 (0.5)	8 (3.1)	14 (2)
Increase–increase	0	0	0	0
Increase–decrease	2 (0.7)	5 (2.6)	5 (2.0)	12 (1.7)
FCP1 or FCP2 missing[b]	83 (30.9)	45 (23.3)	58 (22.7)	186 (25.9)
Low/moderate at baseline, *N* = 355 (49.5%)[a]				
Stable	19 (7.1)	17 (8.8)	20 (7.8)	56 (7.8)
Stable–increase	3 (1.1)	5 (2.6)	6 (2.4)	14 (2)
Stable–decrease	9 (3.3)	9 (4.7)	9 (3.5)	27 (3.8)
Decrease–stable	7 (2.6)	8 (4.1)	8 (3.1)	23 (3.2)
Decrease–increase	4 (1.5)	5 (2.6)	10 (3.9)	19 (2.6)
Decrease–decrease	1 (0.4)	0	1 (0.4)	2 (0.3)
Increase–stable	13 (4.8)	3 (1.6)	10 (3.9)	26 (3.6)
Increase–increase	2 (0.7)	2 (1)	1 (0.4)	5 (0.7)
Increase–decrease	9 (3.3)	6 (3.1)	10 (3.9)	25 (3.5)
FCP1 or FCP2 missing[b]	58 (21.6)	42 (21.8)	58 (22.7)	158 (22)
	269 (100)	**193 (100)**	**255 (100)**	***N* = 717**[a]

Note: Values represent patient numbers (*N*) and valid percentages within result types (%), that is, percentage of the *N* = 717 cases with a valid FCP0 measure and at least one other valid measure (FCP1 or FCP2).

[a]Category at T0 defined by median split based on FCP0 value (Low: <18; High: ≥18). Trend in FCP calculated as change score between T0 to T1 and T1 and T2 and then defined by SD of FCP0 (0.5SD = 4; decrease: ≤-4; stable: >-4 and <+4; increase: ≥+4). *N* = 4 participants have a missing value on FCP0, and hence are not classified in the high versus low/moderate at baseline group. These participants are excluded from this table.

[b]Participants with either a missing value on FCP1 or FCP2.

Abbreviations: FCP, fear of cancer progression; SD, standard deviation; Tx, treatment.

regression model predicting FCP accounted for 48% of the variation in FCP ($R^2 = 0.48$) for T1 and 58% of the variation in FCP ($R^2 = 0.58$) for T2. Compared to having a non-actionable variant, there was evidence that individuals with a variant that was actionable within the MoST study had lower FCP at T1 ($B = -1.79$, $t[399] = -2.01$), $p = 0.045$ ('Not actionable' as reference category). There was no such evidence for result type in predicting FCP at T2.

Hypothesis 3,4: FCP will be associated with socio-demographic and psychological variables and knowledge.

In the regression model (Table 3) predicting FCP at T1, FCP at T0 ($B = 0.61$, $t[399] = 14.12$, $p < 0.001$) and FACIT-Sp at T0 ($B = -0.12$, $t(399) = -2.78$, $p = .006$) were also significant predictor variables. That is, a higher baseline FCP and a lower baseline level of spiritual well-being predicted higher FCP at T1. FCP at T0 ($B = 0.22$, $t(285) = 3.65$, $p < .001$) and at T1 ($B = 0.52$, $t(285) = 8.26$, $p < .001$), FACIT-Sp at T1 ($B = -0.14$, $t[285] = -3.22$, $p = 0.001$), education ($B = -2.12$, $t[285] = -2.17$, $p = 0.031$) and gender ($B = -1.53$, $t[285] = -2.22$, $p = 0.027$) were significant predictors of FCP at T2 (Table S3). That is, higher FCP at T0 and T1 and lower spiritual well-being at T1 predicted higher FCP at T2. Compared to female participants and

TABLE 3 Linear regression analysis predicting fear of cancer progression at T1

Predictor	*B*	SE *B*	*β*	*p*-Value
(Constant)	6.98	4.44	-	0.116
FCP at baseline (T0)	**0.61**	**0.04**	**0.60**	**<0.001**
Age	−0.02	0.02	−0.03	0.426
Sex: Female (ref) versus Male	−0.51	0.64	−0.03	0.419
Marital status: Married (ref) versus Not married	−0.40	0.79	−0.02	0.612
Having children: No (ref) versus Yes	0.19	0.87	0.01	0.825
Speaking English at home: Yes (ref) versus No	0.54	0.89	0.02	0.544
Medical/science occupation: No (ref) versus Yes	−0.36	1.20	−0.01	0.763
Relative with cancer: No (ref) versus Yes	−0.18	0.63	−0.01	0.777
Result type				
Non-actionable (ref) versus Actionable via MoST	**−1.79**	**0.89**	**−0.08**	**0.045**
Non-actionable (ref) versus Actionable other	−0.85	0.70	−0.05	0.225
Education				
≤Secondary (ref) versus Vocational	−0.07	0.90	−0.003	0.939
≤Secondary (ref) versus Undergraduate	−0.33	0.86	−0.02	0.705
≤Secondary (ref) versus Postgraduate	−0.03	0.89	0.002	0.972
Accessibility and remoteness index of Australia				
Remote (ref) versus Major city	3.63	2.81	0.21	0.196
Remote (ref) versus Inner regional	2.74	2.85	0.13	0.338
Remote (ref) versus Outer regional	4.83	2.93	0.18	0.100
Cancer incidence				
Rare (ref) versus Common	0.3	0.79	0.001	0.970
Rare (ref) versus Less common	1.22	0.95	0.05	0.199
Attitude towards uncertainty (T0)	0.51	0.67	0.03	0.448
Knowledge (T0)	0.03	0.02	0.07	0.084
Functional assessment of chronic illness therapy - spiritual well-being (T0)	**−0.12**	**0.04**	**−0.12**	**0.006**
Self-efficacy (T0)	−0.49	0.54	−0.04	0.361
Perceived susceptibility (T0)	0.01	0.01	0.03	0.544

Notes: $R^2 = 0.48$. Bold emphasis highlights the statistically significant result.
Abbreviation: ref, reference category.

those with a secondary educational level, males and those with postgraduate education had lower FCP at T2. Knowledge was unrelated to FCP at T1 or T2.

4 | DISCUSSION

This study, the first to explore FCP patterns in people with advanced (primarily rare) cancers receiving CTGP, showed considerable diversity in FCP. However, FCP was relatively stable over time, with patients' FCP staying either high or low over the 5–6-month study period. Our predictive models of FCP revealed that lower FCP and higher spiritual well-being at previous assessments predicted lower FCP both immediately post results-receipt (T1) and 2 months later (T2). Receiving an actionable result with immediate access to tailored treatment through a MoST clinical trial predicted lower FCP only at T1, while higher education and being male, predicted lower FCP only at T2.

Similar to other studies assessing FCR longitudinally,[13,17–24] we have identified two trajectories (in this case—high stable, low stable). Indeed we find that FCP at the previous assessment was one of the few predictors of FCP at subsequent assessments. This supports previous findings[13,14] which found high-stable FCR to be common in

populations with metastatic disease, not surprising in people who have been told their cancer is no longer curable.

As predicted, the CTGP result impacted patients' FCP. Only when an actionable result was linked to an immediate treatment option did FCP decline at T1. Interviews with MoST participants[32] indicated that those who received an actionable result but were told a trial was *not* available through MoST, believed they were unlikely to be offered an appropriate trial elsewhere. Thus, their hopes of accessing potentially effective tailored treatment were dashed, leaving them vulnerable to renewed FCP.

Two months after result receipt, result type was no longer a significant predictor of FCP. Perhaps the actual result had receded in significance, while ongoing anxiety related to facing a terminal disease became more prominent. At this stage, females and those with lower education were also experiencing more FCP, as has been previously reported, albeit inconsistently.[39]

Another predictor of FCP post-CTGP result and 2 months later, was spiritual well-being. Higher spiritual well-being was associated with lower FCP at both timepoints. This supports a recent study[3] that showed that death anxiety is a key factor in FCP, while a sense of meaning and purpose is associated with lower FCP. Meaning and purpose, peace with one's past, current life and relationships and the future, and faith in a higher being, are all likely to mitigate existential concerns as predicted by Terror Management theory. Spiritual well-being is not commonly assessed in studies of FCR in patients with early-stage cancer, but higher spirituality has been found to be associated with better quality of life in cancer patients regardless of physical deterioration.[40,41]

Our data did not support Social Cognitive and Uncertainty Theories which suggested that self-efficacy in coping with results and attitudes to uncertainty would be associated with FCP. Possibly, results of any type (actionable or non-actionable) reduce uncertainty, thus negating influence of attitudes to uncertainty.[42] Why self-efficacy was not associated with FCP is harder to explain, and contrasts with findings of other studies with general cancer populations.[43] Other patient characteristics such as attributional style, level of optimism and neuroticism, not measured in the current study, may also explain variance in FCP, and could be explored in future studies.

4.1 | Study limitations

Our participants were not undergoing CTGP as part of routine clinical care but within a research programme (the MoST Program). Possibly, their FCP motivated MoST participation, and thus their FCP may have been higher than that of people in routine care and impacted by different factors. However, there is an increasingly blurry line between research and clinical practice within genomics, where the goals of both pursuits, namely best outcomes for patients and generation of new knowledge, may motivate participation. Thus, differences between patients undergoing CTGP in a clinical versus research setting may not be great.

We had only two months follow-up of FCP post results. However, in this very sick population prognosis was poor; numbers remaining at longer follow-up would likely be very small. A significant proportion of patients had missing data from at least one assessment. Those with missing data had worse functional status and higher FCP at the second assessment, and were thus likely sicker, which may have impacted outcomes.

The PiGeOn study was primarily designed to explore psychological responses to CTGP testing, rather than predictors of FCP; other factors known to maintain FCP, such as meta-cognitions, were not measured. As genomics is a relatively new area, context-specific measures are lacking; adapted measures were utilised to capture some responses. Adaptation may have resulted in loss of reliability and validity, which in turn may explain the lack of strong associations we found with FCR.

4.2 | Clinical and research implications

People with high FCP and low spiritual well-being at baseline appear at higher risk of increased FCP post-CTGP result receipt. Patients struggling to find meaning in their illness, and purpose to provide direction at the end of life, may respond more negatively to results that take away hope. Routine screening before and after result receipt for these psychosocial/spiritual characteristics may help to identify patients who may benefit from closer monitoring and provision of psychosocial support. Simple tools for assessing spiritual well-being are available, easily incorporated into routine history taking.[44]

Future studies should explore interventions to best address FCP in patients undergoing CTGP. A recent pilot of a cognitive–existential intervention with cancer survivors by Maheu and colleagues[45] demonstrated high acceptability, although no outcome data were reported. A large multi-centred trial (FORT) is currently underway.[46] This intervention, targeting death anxiety, living with uncertainty and goals for the future, was based on earlier interventions for cancer-related anxiety[47] and is one of few to explicitly address existential issues for patients fearful of progression. This approach, if proven effective, may well complement existing evidence-based interventions, such as recent meta-cognitive approaches[48] for patients with advanced disease.

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CONFLICTS OF INTEREST

BM has a remunerated consultant role with the company AstraZeneca with respect to an unrelated project. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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