ESMO Open Cancer Horizons

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Preferences to receive unsolicited findings of germline genome sequencing in a large population of patients with cancer

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/esmoopen-2019-000619).

To cite: Bijlsma R, Wouters R, Wessels H, *et al*. Preferences to receive unsolicited findings of germline genome sequencing in a large population of patients with cancer. *ESMO Open* 2020;**5**:e000619. doi:10.1136/esmoopen-2019-000619

Received 17 October 2019
Revised 5 December 2019
Accepted 29 December 2019

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ABSTRACT

Background In precision medicine, somatic and germline DNA sequencing are essential to make genome-guided treatment decisions in patients with cancer. However, it can also uncover unsolicited findings (UFs) in germline DNA that could have a substantial impact on the lives of patients and their relatives. It is therefore critical to understand the preferences of patients with cancer concerning UFs derived from whole-exome (WES) or whole-genome sequencing (WGS).

Methods In a quantitative multicentre study, adult patients with cancer (any stage and origin of disease) were surveyed through a digital questionnaire based on previous semi-structured interviews. Background knowledge was provided by showing two videos, introducing basic concepts of genetics and general information about different categories of UFs (actionable, non-actionable, reproductive significance, unknown significance).

Results In total 1072 patients were included of whom 701 participants completed the whole questionnaire. Overall, 686 (85.1%) participants wanted to be informed about UFs in general. After introduction of four UFs categories, 113 participants (14.8%) changed their answer: 718 (94.2%) participants opted for actionable variants, 537 (72.4%) for non-actionable variants, 635 (87.0%) participants for UFs of reproductive significance and 521 (71.8%) for UFs of unknown significance. Men were more interested in receiving certain UFs than women: non-actionable: OR 3.32; 95% CI 2.05 to 5.37, reproductive significance: OR 1.97; 95% CI 1.05 to 3.67 and unknown significance: OR 2.00; 95% CI 1.25 to 3.21. In total, 244 (33%) participants conceded family members to have access to their UFs while still alive. 603 (82%) participants agreed to information being shared with relatives, after they would pass away.

Conclusion Our study showed that the vast majority of patients with cancer desires to receive all UFs of genome testing, although a substantial minority does not wish to receive non-actionable findings. Incorporation of categories in informed consent procedures supports patients in making informed decisions on UFs.

Key questions

What is already known about this subject?

- ► To be able to correctly interpret the genomic landscape of the tumour and hence appropriate treatment, parallel germline DNA analysis is indispensable.
- ► This poses a challenge because germline DNA contains all sorts of potentially relevant information beyond cancer itself, also known as unsolicited findings (UFs).
- ► Little is known about preferences of patients with cancer concerning the return of these UFs of germline DNA sequencing.
- ► UFs in personalised cancer care create challenges for patients and have consequences for their family members.
- ► This prompted us to embark on a large study to identify patient preferences in returning UFs.

What does this study add?

- ► Our study demonstrates in a large population of both curative and palliative patients with cancer that all patients with cancer have a strong propensity towards receiving a wide range of genetic risk information, consistent with the enthusiasm for receiving genetic findings among the general public.
- ► We applied a binning approach of genetic information and it is remarkable that the interest in learning about the different categories of UFs is equally high among curative and advanced-stage patients.
- ► There was a difference between man and women with man being more interested to receive all information available.
- ► However, there also was a substantial group of patients who did not want to be informed.
- ► In addition, 15% of patients changed their mind after receiving more information on UFs.

Key questions

What does this study add?

- Our study is the first large quantitative study to explicitly survey preferences of patients with cancer towards disclosure of UFs to family members in the context of precision medicine.
- Interestingly, the majority of participants opposes the hospital contacting relatives directly to inform them about UFs, indicating that most patients want to act as a gateway between professionals and the patient's family.

How might this impact on clinical practice?

- The results of our study contribute to a better understanding of what patients with cancer consider important unsolicited results.
- These insights provide valuable information for clinicians to guide their patients through the exciting, but also challenging, field of genomic-driven oncology and shared decision making.

BACKGROUND

Advances in genome sequencing have transformed cancer prevention, diagnostics, prognostics and treatment.[1–5] Although small gene panels are commonly used in current daily practice, whole-genome or whole-exome sequencing (WGS/WES) are gaining ground. WGS/WES have many advantages over small targeted gene panels including identification of amplifications, mutational burden and fusion genes and can therefore reveal more and novel genetic targets of therapy compared with small panels.[6–8]

In general, WGS/WES also encompasses sequencing of germline DNA as reference material, in order to aid the interpretation of genomic data of the tumour. However, germline sequencing may reveal findings with consequences that extend beyond providing cancer care for an individual patient. Germline DNA sequencing may identify mutations associated with cancer susceptibility and non-oncological diseases such as neurological or psychiatric illnesses.[3 6 9–11] These findings may have medical, psychological, financial and social implications for patients, and may be relevant for the immediate family members. There is therefore a clear and unmet need to guide patients and oncologists in making informed decisions based on patients' germline genomic information including unsolicited findings (UFs). To facilitate informed decision-making and to prevent patients from being overwhelmed by a long list of potential UFs, it has been suggested to categorise potential findings into clinically meaningful bins. Several frameworks have been proposed that bin UFs into categories based on the extent to which an UF enhances therapeutic or preventive options.[9 12] Based on qualitative interviews with patients with cancer, we previously indicated that such a framework may be helpful in making choices on UFs and provides information on how patients view genetic UFs.[13 14] However, our assumptions are based on relatively small numbers of patients and require confirmation from larger clinical studies. We therefore conducted a large quantitative survey study to investigate how patients with cancer are optimally informed. We also specifically addressed the question whether a binning approach to UFs could be useful as part of a comprehensive strategy to introduce WGS/WES in oncology in an ethically responsible way.

Here, we describe preferences of a large cohort of patients with cancer on how they want to receive genetic (risk) information obtained by WGS/WES and their wish for sharing this information with their family members.

METHODS

From January 2017 until July 2018, patients with cancer were included in the OncoGenEthics study in the Netherlands. Participants were recruited from 10 hospitals, affiliated with the Center of Personalized Cancer Treatment, a consortium of 49 hospitals in the Netherlands. During an outpatient visit, patients with cancer were offered an envelope by their oncologist containing an invitation to participate in the survey as well as background material to inform them about the aim of the study.

Respondents were assured that their answers would be kept confidential and that the data would be processed anonymously. Inclusion criteria were: age 18 years or older, diagnosed with cancer (any stage and origin of disease) and ability to read Dutch. In addition, participants of two Dutch longitudinal cohorts (the prospective Dutch colorectal cancer cohort and the Utrecht Cohort for Multiple Breast Cancer Intervention Studies and Long-term Evaluation were invited by email.[15 16]

Informed consent was obtained from all participants. After reading background information, patients could accept inclusion in the study either by sending an email or a reply postcard included in the provided information envelope.

A link to the online survey was send to all the applicants. The online questionnaire was based on previous qualitative research involving semi-structured interviews with patients with cancer.[13] The survey included sociodemographic questions, questions concerning patients' experiences with genetics and tumour profiling and questions to assess health literacy.[17–19]

To ensure that participants had sufficient and the same background knowledge, two digital videos were included in the questionnaire, the first video introduced basic concepts of genetics and the second video provided neutrally worded information on the potential impact of receiving UFs and information on four different categories of UFs (actionable UFs, non-actionable UFs, UFs of reproductive significance, UFs of unknown significance, respectively, figure 1 (online supplementary videos 1 and 2)).[13] Finally, anxiety and depression were assessed using the validated Dutch version of the self-report Hospital Anxiety and Depression Scale (HADS).[20 21] Health-related quality of life was measured by the validated, Dutch translation of the 30-item European Organisation for Research and Treatment of Cancer-Quality of Life-C30 questionnaire.[22] The complete questionnaire in Dutch is accessible via https://tinyurl.com/yc9yfb7k.

All patient data were encrypted and processed anonymously. Patients received a reminder 2, 3 and 16 weeks

Category 1: Actionable UFs	**Category 2:** Non-actionable UFs	**Category 3:** UFs of reproductive significance	**Category 4:** UFs of unknown significance
A gene variant that predisposes you to a disease that can be prevented or treated.	A gene variant that predisposes you to a disease that cannot be prevented or for which no current effective treatment has been established yet.	A gene variant that does not affect your health, but that may be important to the health of your other relatives, such as your children or future offspring.	Uncertain gene variants, meaning they may or may not be important to your health or the health of your relatives.
Example: you have a gene variant which means you are much more likely to develop breast cancer. In this case, we may recommend that you more closely monitor your breasts or have prophylactic surgery	*Example:* you have a gene variant which implies that you are more likely to develop Alzheimer's disease. Alzheimer's disease cannot be treated or prevented	*Example:* you could learn that you have a variant in the gene that may cause Cystic Fibrosis (CF) in future offspring if the other parent would have this variant in her or his gene too.	*Example:* you have a so-called unclassified variant, which implies you do have a variant for example for an increased risk of breast cancer, but the significance is unknown.

Figure 1 Four categories of unsolicited findings. UF, unsolicited finding.

after inclusion in the study if they had not yet completed the questionnaire.

Data analysis

The data were analysed using Statistical Package for the Social Sciences, V.25 (SPSS, Chicago, Illinois, USA). For univariable analysis, Pearson's χ^2 test and analysis of variance were used to test whether participant characteristics were correlated with preferences regarding UFs. Furthermore, binary logistic regression was used to calculate ORs and 95% CIs to study whether relevant patient characteristics were associated with different preferences, corrected for other variables. Data from participants who stopped before completing the questionnaire were included in the analysis up to the point that they quitted, in order to preserve their data. As a result, the total number of participants included in the analyses differs from one question to another. Percentages and ORs were calculated based on the number of participants who answered the specific question.

RESULTS

Response

A total of 1072 patients with cancer indicated by postcard or email that they were willing to participate. Furthermore, 95 patients also returned the postcard indicating that they did not want to participate, for example, because they were too ill (n=36; 38%), did not have access to the internet (n=11; 12 %) or were not interested in the topic (n=15; 16%). In total, 845 patients started the survey and 701 participants completed the whole questionnaire, which lasted about 1 hour to complete. In figure 2, the survey inclusion and participant numbers are shown. Patients characteristics are shown in table 1.

Preferences for receiving genetic information

At the start of the survey, 686 participants (85.1%) indicated that they would like to be informed about UFs. After the second video was shown, explaining that UFs can be divided into four different categories (actionable UFs, non-actionable UFs, UFs of reproductive significance and UFs of unknown significance), participants were asked specifically whether they would like to receive each of these categories of unsolicited information. After viewing this video, a statistically significant number of participants (113 of 764 (14.8% 95% CI (12.3% to 17.3%)) changed their answer on the general question whether they want to receive UFs: 59 (7.7%) patients of the total group participants changed their answer from wanting to receive into not wanting to receive any UFs at all and 54 (7.1%) participants changed their answer from not wanting to receive into wanting to receive UFs.

Overall, 718 participants (94.2%) wanted to be informed about actionable variants, 537 (72.4%) wanted to receive information on non-actionable variants, 635 (87.0%) were interested to receive information on variants of reproductive significance and 521 (71.8%) participants would also like to receive information on variants of unknown significance. Throughout all categories, no statistically significant differences were found between preferences of curative participants and advanced-stage participants. In table 2, selection of our univariable analysis is presented, the complete univariable analysis is presented in online supplementary table 1 (available at: https://tinyurl.com/ycbb3dz7). Statistically significant more men than women chose to receive UFs, especially regarding non-actionable UFs (279 (82.1%) men vs 258 (64.2%) women) and UFs of unknown significance (263 (87.7%) men vs 258 (65.8%) women). Age and education were not associated with preferences (in general and all categories).

Multivariable analysis of subgroups

Multivariable logistic regression analysis (table 3) demonstrated that men were more willing to receive UFs compared with women (non-actionable: OR 3.32; 95% CI 2.05 to 5.37) (reproductive significance: OR 1.97; 95% CI 1.05 to 3.67); (unknown significance: OR 2.00; 95% CI 1.25 to 3.21).

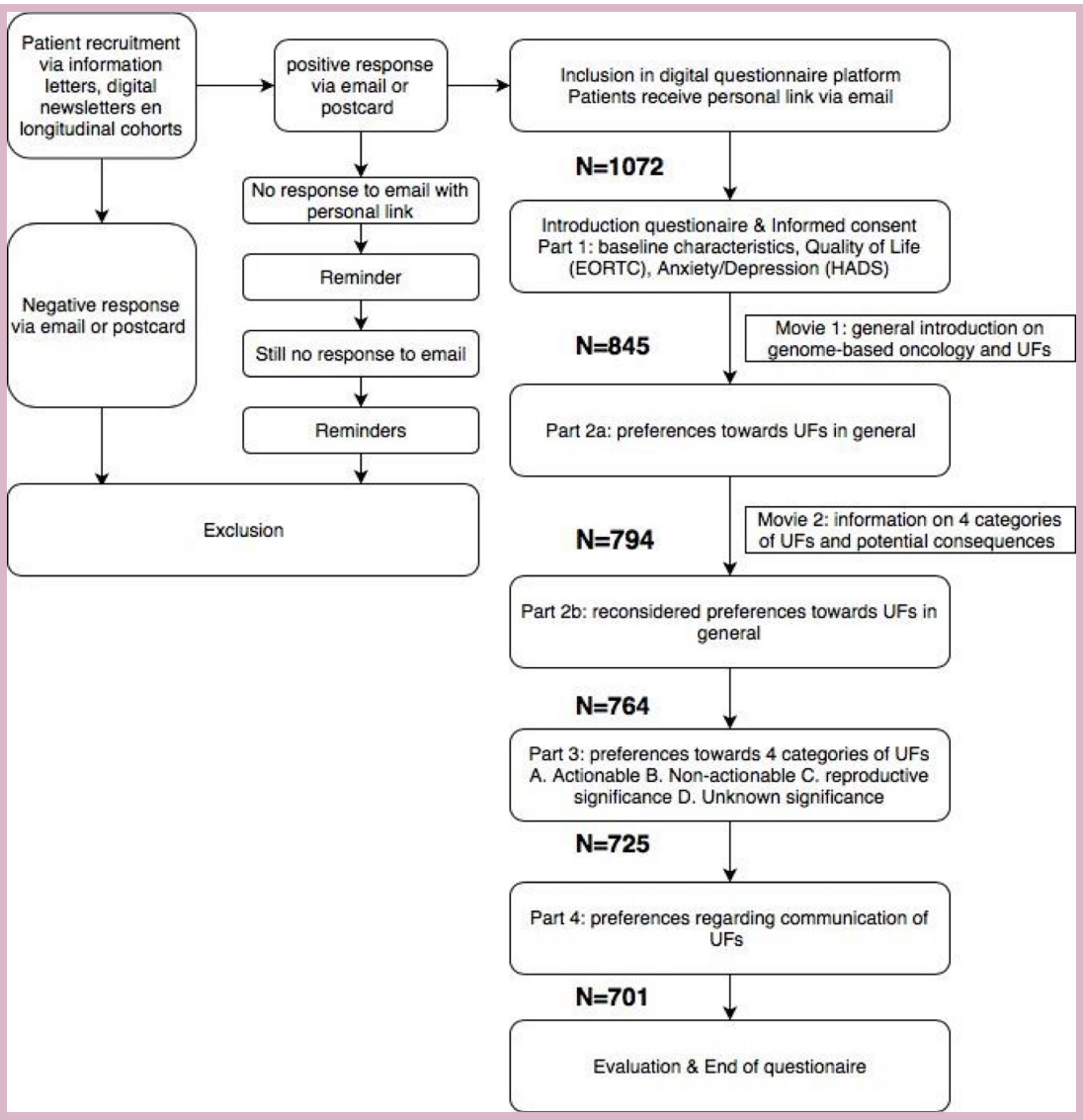

Figure 2 Survey questionnaire inclusion and participant numbers. EORTC, European Organisation for Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale; UF, unsolicited finding.

Initially, curative participants were less likely to be willing to receive UFs (OR 0.56; 95% CI 0.32 to 0.99), however, when providing the four different categories of UFs, the difference with regard to the return of UFs between curative and advanced-stage participants disappeared.

College degree was associated with higher preference of receiving actionable UFs (OR 2.31; 95% CI 1.02 to 5.22) and lower preferences for receiving UFs of unknown significance (OR 0.59; 95% CI 0.41 to 0.85). Participants with living first-degree or second-degree family members were more interested in receiving UFs of reproductive significance. For participants with children, this finding was statistically significant (OR 5.05; 95% CI 2.97 to 8.58). Participants with a religious conviction turned out to be less willing to receive non-actionable UFs (OR 0.54; 95% CI 0.38 to 0.79) than participants without a religious conviction.

For cancer subtypes, only participants with urogenital cancer had different preferences, among others less willingness to receive non-actionable UFs (OR 0.47; 95% CI 0.22 to 0.99) and UFs of unknown significance (OR 0.40; 95% CI 0.19 to 0.83).

Participants with elevated levels of anxiety or depressive feelings (defined as HADS score >13) were less inclined to receive actionable UFs (OR 0.89; 95% CI 0.82 to 0.97) and patients with a higher quality of life were in general more interested in receiving UFs (OR 1.02; 95% CI 1.00 to 1.03), especially for UFs of unknown significance (OR 1.01; 95% CI 1.00 to 1.02). ORs were based on per point quality of life increase, and since the scores range from 30 to 100, these ORs are clinically meaningful.

Sharing information with family members

Thirty-three per cent (n=244) of participants wanted family members to have access to their UFs while the patient is still alive, and 30% (n=221) of participants wanted the hospital to actively contact family members without the intervention of the patient. After passing

Table 1 Patient characteristics

Characteristic		N (%)
Gender	Male	386 (45.7%)
	Female	455 (53.9%)
Cancer stage	Curative	311 (37.5%)
	Advanced	519 (62.5%)
Mean age, year (SD)	All participants	59.9 years (11.1)
Age, years	18–35	30 (3.6%)
	36–50	113 (13.4%)
	51–65	414 (49.1%)
	66–79	273 (32.3%)
	≥80	11 (1.3%)
Country of origin	The Netherlands	754 (90.7%)
	Other*	77 (9.3%)
Educational level	No college degree	413 (49.1%)
	College degree	428 (50.9%)
Family composition	Partner	713 (85.0%)
	Children	662 (78.7%)
	Siblings	793 (94.3%)
Religious conviction	Religious conviction	287 (34.0%)
	No religious conviction	557 (66,0%)
Cancer type	Colorectal cancer	318 (38.0%)
	Breast cancer	259 (31.0%)
	Urogenital cancer (bladder, renal, prostate, testicular)	86 (10.3%)
	Melanoma	38 (4.5%)
	Gynaecological cancer (cervical, ovary, uterine)	29 (3.5%)
	Lung cancer	22 (2.6%)
	Upper GI cancer (oesophageal, stomach)	19 (2.3%)
	Sarcoma	16 (1.9%)
	Brain tumour	14 (1.7%)
	Other	20 (2.4%)
Time to cancer diagnosis	<1 year after diagnosis	272 (32.7%)
	≥1–2 years after diagnosis	216 (26.0%)
	≥2 years after diagnosis	344 (41.3%)
Treatment site	University Medical Centers and Netherlands Cancer Institute	460 (54.9%)
	Non-academic hospital	378 (45.1%)
Perceived health literacy	Adequate	807 (96.6%)
	Inadequate	28 (3.4%)
Self-reported knowledge about DNA and genetics	Sufficient	290 (34.7%)
	Not sufficient	450 (53.8%)
	Do not know	96 (11.5%)

*At least one of the parents is not born in the Netherlands.

away, this significantly increased to 82% (n=603) and 76% (n=558) of participants would be willing to give permission to share the genetic data. Table 4 shows participants' preferences with respect to sharing information with family members.

DISCUSSION

Our study shows that a vast majority (85.1%) of the total group patients with cancer when asked to participate in genomics-guided treatment in the Netherlands prefers to receive UFs as complete as possible. Almost all participants desired disclosure of information that gives rise to preventive or therapeutic options and information on genomic aberrations that cause recessive disorders. A majority (72.4%) of the total group participants would also opt for feedback of findings that presently are considered to be non-actionable (category 2). Nevertheless, there is a substantial group (20.6%) of participants who does not wish to be informed about these category 2 non-actionable UFs. The same is true for variants of unknown significance of category 4, where 18.2% of participants do not wish to be informed. The percentage of participants who wished to receive information that is non-actionable or of uncertain significance is significantly lower than the percentage of participants who wished to receive information that is actionable or of reproductive significance, especially among female participants.

The finding that the majority of participants would like to get feedback on every category of genetic information sheds new light on the management of UFs and is remarkable from the perspective that sharing genetic information is typically approached with great caution. Our study is the first to demonstrate in a large population of both curative and palliative patients with cancer that the majority of patients want to learn about a wide range of genetic risk information, consistent with the enthusiasm for receiving genetic findings among the general public and with smaller studies among patients with cancer.[23–25] It is also remarkable that the interest in learning about the different categories of UFs is equally high among curative and advanced-stage patients. Apparently, life expectancy is not a decisive factor for patients in embracing genetic information. Although concerns about insurability have been reported in other studies, including a qualitative study from our own group, these concerns do not seem to have a bearing on the results of our current large survey study.[13]

Our study gives valuable guidance to patients and oncologists on how to shape what is known as an 'anticipate or communicate' approach: anticipate that UF will occur if a large group of patients will be sequenced and communicate policies on how UFs are handled to patients before the sequencing takes place.[6 26–29] The current results provide oncologists with tools for a personalised approach to informed consent by giving patients the opportunity to choose between meaningful categories, as opposed to an all-or-nothing approach in which professionals preselect a subset of UFs.[30] While 85% of

Table 2 Univariable analysis of the question whether or not to receive unsolicited findings (UFs)

Question	Answer	Total group (number of patients/%)	Gender (number of patients/%)		Stage (number of patients/%)	
			Male	Female	Curative	Advanced stage
In general, if (again) a genetic tumour	Do not want to know	67 (8.3%)	31 (8.3%)	36 (8.3%)	45 (9.0%)	22 (7.5%)
profile is determined then I want to be	Neutral	53 (6.6%)	21 (5.7%)	32 (7.4%)	38 (7.6%)	15 (5.1%)
informed about unsolicited findings	Want to know	686 (85.1%)	319 (86.0%)	367 (84.4%)	417 (83.4%)	258 (87.5%)
			P=0.625		P=0.267	
If (again) a genetic tumour profile is	Do not want to know	24 (3.2%)	10 (2.9%)	14 (3.4%)	15 (3.2%)	9 (3.2%)
determined then I want to be informed	Neutral	20 (2.6%)	12 (3.4%)	8 (1.9%)	9 (1.9%)	11 (3.9%)
about unsolicited findings that may emerge	Want to know	718 (94.2%)	327 (93.7%)	391 (94.7%)	444 (94.9%)	263 (92.9%)
from category 1: actionable UFs			P=0.405		P=0.269	
If (again) a genetic tumour profile is	Do not want to know	153 (20.6%)	47 (13.8%)	106 (26.4%)	103 (22.7%)	49 (17.7%)
determined then I want to be informed	Neutral	52 (7.0%)	14 (4.1%)	38 (9.5%)	27 (5.9%)	23 (8.3%)
about unsolicited findings that may emerge	Want to know	537 (72.4%)	279 (82.1%)	258 (64.2%)	324 (71.4%)	205 (74.0%)
from category 2: non-actionable UFs			**P<0.001**		P=0.163	
If (again) a genetic tumour profile is	Do not want to know	58 (7.9%)	25 (7.4%)	33 (8.4%)	40 (9.0%)	18 (6.6%)
determined then I want to be informed	Neutral	37 (5.1%)	10 (3.0%)	27 (6.9%)	24 (5.4%)	12 (4.4%)
about unsolicited findings that may emerge	Want to know	635 (87.0%)	302 (89.6%)	333 (84.7%)	382 (85.7%)	243 (89.0%)
from category 3: UFs of reproductive significance			P=0.046		P=0.420	
If (again) a genetic tumour profile is	Do not want to know	132 (18.2%)	44 (13.2%)	88 (22.4%)	85 (19.1%)	45 (16.7%)
determined then I want to be informed	Neutral	73 (10.0%)	27 (8.1%)	46 (11.7%)	47 (10.6%)	24 (8.9%)
about unsolicited findings that may emerge	Want to know	521 (71.8%)	263 (78.7%)	258 (65.8%)	313 (70.3%)	201 (74.4%)
from category 4: UFs of unknown significance			**P=0.001**		P=0.493	

Values in bold have a Pearson's χ^2 p value <0.05.

participants initially responded positively to the question as to whether they desired disclosure of UFs in general, percentages in favour of disclosure of separate categories ranged from 72% (UFs of unknown significance) to 94% (actionable findings).

A binning approach to UFs allows patients to accept actionable findings and at the same time to refuse non-actionable or uncertain findings. Binning helps a considerable minority of patients who do not wish to know everything, especially women would benefit from differentiating between categories of UFs along these lines.

Our study also highlights the need to educate patients with cancer on basic genetics and UFs prior to obtaining informed consent. Even in a relatively well-educated study population, only 34.7% of the participants indicated that they had sufficient knowledge about DNA and genetics to make decisions about UFs. One out of seven participants changed their opinion after the second video introduced more information on the potential impact of receiving UFs and an explanation of the four different categories. This is consistent with previous reports and underscores the importance of providing adequate background information.[13 23 24 31]

We propose that distinguishing between the four categories is a good starting point to develop a workflow that enables patients to make well-informed decisions, by streamlining information according to a menu of UF categories that patients can subsequently choose from. Previously, we have suggested that the four-category approach can be complemented by setting opt-in or opt-out defaults.[13] The results of our study could be used to decide which UFs should be communicated on an opt-in and which on an opt-out basis. However, the line between nudging and pushing patients towards a decision is precariously thin, and the effects of any opt-in/opt-out nudging strategy should be carefully considered and evaluated.

Table 3 Multivariate analysis of patient characteristics, basic demographics, disease and social characteristics for patients wanting to receive unsolicited findings (UFs)

	UFs in general			Category 1: actionable UFs			Category 2: non-actionable UFs			Category 3: UFs of reproductive significance			Category 4: UFs of unknown significance		
		95% CI for Exp(B)			95% CI for Exp(B)			95% CI for Exp(B)			95% CI for Exp(B)			95% CI for Exp(B)	
	Exp(B)	Lower	Upper	Exp(B)	Lower	Upper	Exp(B)	Lower	Upper	Exp(B)	Lower	Upper	Exp(B)	Lower	Upper
Male	1.44	0.80	2.61	0.85	0.35	2.07	**3.32**	2.05	5.37	**1.97**	1.05	3.67	**2.00**	1.25	3.21
Age (/years)	1.01	0.99	1.03	0.97	094	1.01	1.01	0.99	1.03	0.98	0.96	1.01	1.01	1.00	1.03
College degree	0.72	0.45	1.14	**2.31**	1.02	5.22	0.79	0.54	1.15	1.00	0.61	1.64	**0.59**	0.41	0.85
Partner	1.13	0.59	2.17	0.32	0.07	1.44	0.95	0.56	1.62	1.23	0.67	2.24	1.27	0.76	2.13
Curative	**0.56**	0.32	0.99	1.05	043	2.57	0.84	0.54	1.30	0.61	0.34	1.10	0.75	0.48	1.16
Reference=other cancer diagnosis	1.00			1.00			1.00			1.00			1.00		
Breast cancer	1.30	0.61	2.77	3.37	0.90	12.58	1.25	0.70	2.26	1.20	0.54	2.67	0.92	0.50	1.67
Colorectal cancer	1.37	0.64	2.91	2.06	0.70	6.11	1.07	0.59	1.93	1.02	0.46	2.25	1.26	0.70	2.30
Urogenital cancer	0.44	0.19	1.03	0.96	0.24	3.79	**0.47**	0.22	0.99	0.45	0.17	1.19	**0.40**	0.19	0.83
Reference=<1 year after cancer diagnosis	1.00			1.00			1.00			1.00			1.00		
1–2years after cancer diagnosis	1.18	0.63	2.22	2.04	0.70	5.98	1.41	0.86	2.32	0.85	0.46	1.58	1.54	0.94	2.52
>2years after cancer diagnosis	0.86	0.47	1.55	1.90	0.75	4.83	1.06	0.66	1.70	1.45	0.78	2.72	1.11	0.69	1.77
Religious	1.02	0.63	1.64	0.63	0.30	1.34	**0.54**	0.38	0.79	1.06	0.64	1.76	0.77	0.53	1.12
Adequate health literacy	0.71	0.15	3.33	1.17	0.27	5.16	1.20	0.42	3.47	2.34	0.73	7.50	1.07	0.35	3.22
With children	1.03	0.58	1.81	1.29	0.48	3.48	1.26	0.80	1.98	**5.05**	2.97	8.58	0.66	0.41	1.05
With siblings	1.34	0.53	3.40	0.00	0.00	.	0.52	0.21	1.31	0.33	0.08	1.49	1.29	0.60	2.77
Autochthonous*	0.70	0.30	1.64	2.69	0.92	7.91	0.91	0.49	1.69	0.82	0.36	1.88	0.95	0.52	1.76
Treated in tertiary hospital+	1.09	0.65	1.81	1.29	0.55	3.06	1.00	0.67	1.50	1.09	0.64	1.86	1.17	0.78	1.73
Total score HADS	1.03	0.97	1.09	**0.89**	0.82	0.97	0.98	0.94	1.03	0.98	0.92	1.04	1.02	0.98	1.07
EORTC Score Global health status/Quality of Life	**1.02**	1.00	1.03	0.99	0.97	1.01	1.00	0.99	1.01	1.00	0.99	1.02	**1.01**	1.00	1.02

Values in bold have a p value <0.05.
*The Netherlands as country of origin+not a University Medical Center or Netherlands Cancer Institute.
EORTC, European Organisation for Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale.

Table 4 Patient's preferences about sharing information with family members

Patient's preferences	Answer	Category 1	Category 2	Category 3	Category 4
I want my family to have access to unsolicited findings from category … of the genetic research, *without intervention of myself.*	Completely disagree	431 (57.5%)	453 (61.7%)	402 (55.4%)	440 (60.7%)
	Neutral	61 (8.2%)	53 (7.2%)	61 (8.4%)	57 (7.9%)
	Completely agree	257 (34.3%)	228 (31.1%)	263 (36.2%)	228 (31.4%)
I want the hospital to actively seek contact with my family, if unsolicited findings (which are relevant to them) from category … emerged from genetic research, *without intervention of myself*.	Completely disagree	479 (64.0%)	461 (62.8%)	417 (57.4%)	437 (60.2%)
	Neutral	63 (8.4%)	64 (8.7%)	60 (8.3%)	70 (9.7%)
	Completely agree	207 (27.6%)	209 (28.5%)	249 (34.3%)	218 (30.1%)
I want my family, *after my death*, gain access to the unexpected results from category … of genetic research.	Completely disagree	73 (9.7%)	87 (11.9%)	95 (13.1%)	91 (12.5%)
	Neutral	41 (5.5%)	51 (6.9%)	39 (5.4%)	47 (6.5%)
	Completely agree	635 (84.8%)	596 (81.2%)	592 (81.5%)	587 (81.0%)
I want the hospital, *after my death* (also years later, when new insights appear) actively seek contact with my family, if unsolicited findings (which are relevant to them) from category … emerged from genetic research.	Completely disagree	87 (11.6%)	119 (16.2%)	114 (15.7%)	109 (15.1%)
	Neutral	71 (9.5%)	77 (10.5%)	57 (7.9%)	69 (9.5%)
	Completely agree	591 (78.9%)	538 (73.3%)	555 (76.4%)	547 (75.4%)

To our knowledge, this study is the first large quantitative study to explicitly survey preferences of patients with cancer towards disclosure of UFs to family members in the context of precision medicine. The majority of participants opposes the hospital contacting relatives directly to inform them about UFs, indicating that most patients want to act as a gateway between professionals and the patient's family. Previous studies showed mixed results regarding family disclosure.[32] Our findings have important implications for the debate that revolves around family dilemmas that arise from genomic testing. While some have emphasised the professional's duty to warn family members that they are at risk for (treatable or preventable) hereditary diseases, others have argued that direct communication would breach patient-physician confidentiality or would impose excessive burdens on healthcare resources.[33] Our results show that many patients cherish the protection of their genetic privacy even after being specifically informed about the significance of genetic information to their family members' health. However, a policy that allows family members to retrieve UF results after the patient has passed away could draw substantial support among patients with cancer. Currently, there is no legal precedent in the Netherlands to breach the physician-patient confidentiality. As we expect genetic sequencing to be more and more available, especially in cancer care, our study shows that the majority of participants would agree to disclose their genomic data to their family members. This will pave the way for procedures that will allow relatives to obtain access to the germline data with the consent of the patient.

Our study also has limitations. First, the study population is not completely representative of the Dutch population because of some imbalance in educational level (50.9% participants have a college degree compared with 28.5% in the general Dutch population) and country of origin (9% of study participants were migrant patients compared with 21% in the general Dutch population).[34] Furthermore, almost all participants are thought to have appropriate health literacy. However, we found that the major findings of our study are upheld when adjusting the analyses for the level of education and health literacy. Second, most of the participants in this study have no actual experiences with WGS. In other words, most preferences reported in this study are hypothetical preferences, which may differ from actual preferences. Third, not all participants succeeded to complete the extensive questionnaire.

In conclusion, our study has several clinical implications. First, as the return of UFs is desired by almost all participants, implementing a policy that allows careful communication of genetic information to patients is recommended in order to be responsive towards patients' needs. Second, a substantial minority of the participants does not wish to be informed about at least one of the four categories that we proposed. Therefore, we recommend a tiered informed consent procedure in which patients can choose between four categories and we recommend extensive background information. Third, our study dictates caution with respect to providing information on UFs to family members, at least when participants are still alive.

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Acknowledgements The authors would like to thank the patients with cancer for their willingness to participate in this study. The authors would like to thank the Center of Personalized Cancer Treatment (CPCT) and two Dutch observational cohorts for their collaboration: the prospective Dutch colorectal cancer cohort (in Dutch: 'Prospectief Landelijk ColoRectaal kanker Cohort' (PLCRC) and the Utrecht Cohort for Multiple Breast Cancer Intervention Studies and Long-term Evaluation (UMBRELLA).

Contributors All authors have declared no conflicts of interest.

Funding This work was supported by the Dutch Cancer Foundation (KWF), grant UU2014-7469.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The research protocol was approved by the Research Ethics Committee of the University Medical Center Utrecht, The Netherlands.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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