Unsolicited genetic findings in clinical oncology

Cancer patients' needs and preferences in the era of DNA sequencing

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Onverwachte genetische bevindingen in de oncologie
De behoeften en voorkeuren van patiënten met kanker in de tijd van DNA-sequencing
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 9 januari 2019 des middags te 2.30 uur door

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Voor Ward,

Voor Annelie, Laurens en Liselot,

de grote liefdes van mijn leven

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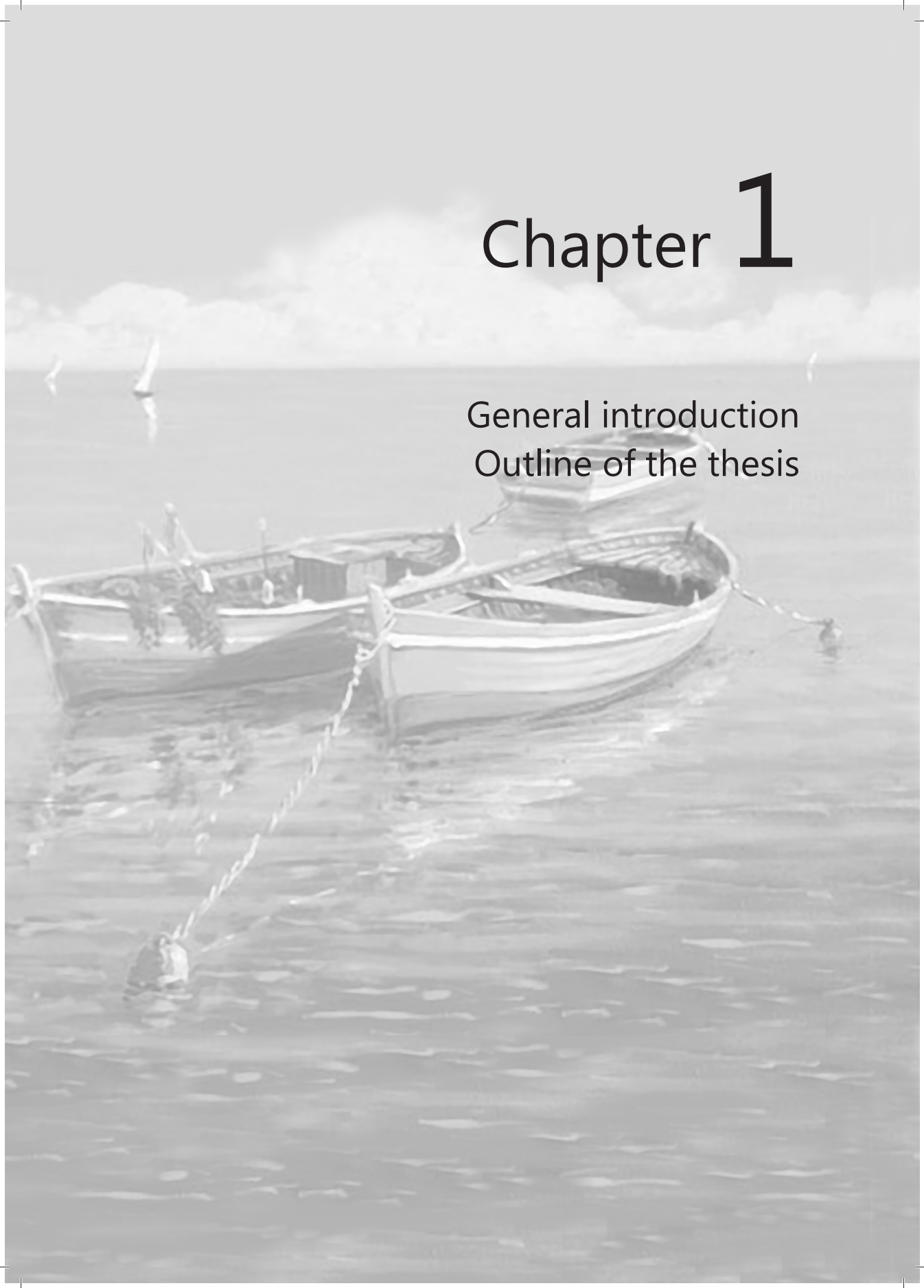

Chapter 1

General introduction
Outline of the thesis

General introduction

With the rapid advancement of sequencing technologies it is now possible to sequence whole genomes in a short period of time. The excitement surrounding the implementation of DNA sequencing in clinical daily practice comes largely from the belief that discoveries from cancer genome sequencing have the potential to translate into advances in cancer prevention, diagnostics, prognostics and treatment.[1,2,3,4] Oncologists are increasingly receiving DNA sequencing results concerning their patients. Interpretation of these genetic test results is part of a personalized cancer treatment: the use of large-scale genetic analyses of tumors is considered to be crucial for a better selection of patients for the appropriate anti-cancer drug therapy.

Reliable genetic variants discovered as a research product are reviewed in multidisciplinary teams consisting of bioinformaticians, pathologists, medical oncologists, researchers, molecular geneticists and clinical geneticists to discuss possible actionable somatic mutations. These advances in technology more than ever emphasize the need for good communication and collaboration between the healthcare professionals involved.

Although a powerful diagnostic tool, these sequencing technologies at the same time generate large amounts of both solicited and unsolicited genetic (risk) information. By sequencing both tumor and germline DNA, one could encounter unrelated DNA changes that warrant additional attention. Mutations may be encountered that are associated with increased susceptibility not only to the disease under study but also to other hereditary cancer syndromes and other diseases, such as neurological or psychiatric illnesses.[4,5,6,7]

DNA sequencing potentially brings a deluge of genetic (risk) information with it, including genetic data that are solicited and unsolicited, validated and not validated, highly and poorly predictive and more or less probabilistic.[7] These findings could have medical, psychological, financial and social consequences for the patient and could also have a considerable impact on the patient's quality of life. Moreover, these findings may also be relevant for family members.

Genetic testing

It is important to realize that differences exist between germline genetic testing at the department of clinical genetics and the somatic tumor testing in the context of an oncological treatment.

In the current cancer genetic counseling setting, the extensive pre- and post-test genetic counseling procedure under the care of a clinical geneticist provides patients with the opportunity to be well informed and to participate in the decision to proceed with the genetic testing for hereditary cancer syndromes.[8] Interpretation of the germline genetic test results is carried out by a certified laboratory and once a germline mutation is detected, communication to family members is supported by the accompanying clinical geneticist.

In the context of research, DNA sequencing will also offer an analysis of multiple susceptibility genes; however, in-depth pre-test counseling in research tumor testing is often lacking. When a genetic germline variant is suspected, validation of the detected variant in a second blood sample carried out by a certified laboratory is necessary. Subsequently, a referral to a clinical geneticist is recommended because only a minority of genetic variants are of clinical importance.
Hence, due to the rapid developments of sequencing technologies, it is possible to sequence larger panels of genes that may be involved in cancer susceptibility. Clinicians other than the clinical geneticist are increasingly confronted with these new technologies, and should become able to interpret and understand the results and communicate the results to their patients.[9]

Ethical and counseling dimensions

Recent studies suggest that patients and their family members want to be informed about the unsolicited findings in somatic and germline DNA.[6,10] However, it is unknown whether this desire is the same in healthy people and cancer patients, and whether differences exist between curable or advanced-stage patients. Moreover, how and by whom these unexpected results should be communicated is not clear yet either.
The question of whether and to what extent genetic research results should be returned to study participants has become one of the most urgent and extensively debated ethical issues in genetics.[11] This debate has taken place mainly in the research context, but it is increasingly relevant for clinical applications of DNA sequencing. It demands continuous attention now that DNA sequencing is entering the "clinical genomics" era, particularly in the field of cancer care.[12,13] Here, we refer to genetic research results as a collective term, but it is important to be aware of the distinction between solicited research findings and 'unsolicited' findings. Although both relate to an individual person, a genetic research finding is generated in a specific study context; it is a confirmation of a specific genetic variant. In contrast, unsolicited findings are discovered unintentionally, as a by-product of a research question.[14,15]
Clearly, the latter will pose additional counseling challenges because cancer patients involved with DNA sequencing in the context of research participation may be confronted not only with cancer susceptibility syndromes, but also with mutations in cancer genes not related to the phenotype and, on top of this, also with genetic risk factors associated with completely different disorders such as dementia and Parkinson's disease.[6] Moreover, patients and study participants, especially in cancer care, could die during the course of the study. Thus, whether to disclose individual results from DNA sequencing to deceased patients' relatives needs to be addressed too.[16,17,18]
For a decision to qualify as autonomous, a person should have a sufficient (degree of) understanding, a sufficient degree of noninterference, and the decision should be reasonably in line with one's personal values and beliefs. This means that a patient should understand what range of possible findings DNA sequencing may generate, and subsequently decide

whether, and if so, what kind of genetic information he would like to receive.[11] In addition, once the patient receives this information he should be capable of absorbing it. Disclosure of DNA sequencing data challenges autonomous decision-making and obtaining an adequate informed consent is clearly challenging, not only for the patient but also for health care professionals.

The debate on whether to reveal genetic research results to study participants/patients has been dynamic, and various opposing viewpoints have been expressed.[5]

A first key ethical challenge involves the physician's responsibility concerning unsolicited findings. The possibility of detecting an unsolicited finding should be discussed with the patient, for example by the treating healthcare professional or the study investigator, during the informed consent procedure. However, at the time of obtaining informed consent, it is difficult to foresee all possible results.[19]

Patients whose whole genome has been sequenced and who did not receive pretest counseling or appropriate clinical interpretation could mistakenly consent to highly sensitive surveillance strategies, or even undergo preventive surgical procedures.[20] Researchers and clinicians have to avoid this so-called "therapeutic misconception" in overestimating the clinical significance of the research findings.[21]

A second ethical challenge stems from the fact that genetic data may gain significance in the course of scientific progress. This raises questions about whether the patient should be (re)contacted at a later stage and whose responsibility this would be.

A third ethical challenge is that the physician has a duty to respect the patient's right not to know.[22,23] In case the right not to know is exercised by the patient, can or should family members be informed to prevent serious harm without consulting the patient? It must be taken in account that sharing information with family members may conflict with patients right not to know unsolicited findings.[24,25] In addition, the interests of relatives can put the autonomy of the individual patient under pressure.[26,27]

Next, causing (psychological) harm as a side effect of returning results to patients is a key concern of genetic health care professionals as the results could create stress and anxiety.[28] Furthermore, the American College of Medical Genetics and Genomics' statement on clinical exome/genome sequencing added a new element to the debate. It proposed routinely offering to test patients who undergo DNA sequencing for a list of 56 disease genes, thereby suggesting that there might be 'a duty to hunt' for genetic risk information.[29]

However, at the start of this thesis there seems to be growing support for the view that at least some genetic results should be offered to research participants; thus, there is an emerging duty to return results. A proposed solution is a qualified disclosure policy that includes predefined packages of information as a way of returning results.[6,11]

This thesis: an investigation of cancer patients' intentions, needs and preferences with regard to receiving unsolicited genetic risk information

Clearly, tumor DNA sequencing raises many ethical and counseling challenges that need to be addressed before it becomes routine clinical practice. Should germline genetic risk information generated by sequencing procedures be disclosed to patients? And if so, what kind of information, and by whom? And what about their family members? How should this information be dealt with if a patient passes away?

There is an emerging international ethical consensus that at least some sets of genetic information should be offered to patients. Although empirical studies confirm that patients prefer to receive this information, these – often US-based – studies have not specifically investigated both curable and advanced-stage cancer patients' preferences.[30,31] There is still little knowledge on cancer patients' intentions, needs and preferences regarding this area.

Research questions of this thesis

This thesis aims to examine cancer patients' intentions, needs and preferences with regard to receiving (unsolicited) genetic (risk) information obtained by sequencing and to sharing this information with their family members.

The research in this thesis focuses on the following research questions:

I. What are cancer patients' intentions, needs and preferences with regard to receiving (unsolicited) genetic information obtained by DNA sequencing and to sharing this information with their family members?

II. To what extent are these results confirmed in a larger group of cancer patients and do differences exist between patient subgroups?

III. What are important ethical considerations for a responsible DNA sequencing practice in clinical oncology?

Outline of this thesis

The research described in this thesis focuses on cancer patients' intentions, needs and preferences with regard to receiving unsolicited genetic information obtained by tumor DNA analysis. We combine qualitative research and quantitative research methods with a normative ethical reflection on the introduction of DNA sequencing into daily practice in clinical oncology.

In **Chapter 2** we describe ethical and organizational aspects regarding the management of unsolicited findings in personalized cancer research and treatment, illustrated by a description of three patients faced with an unsolicited DNA finding.

To address our first research question, a group of cancer patients (both curative and advanced stage, any cancer type) was invited to participate in in-depth, semi-structured interviews to learn their intentions, needs and preferences. The results of this qualitative research are presented in **Chapter 3**, in which we describe cancer patients' attitude and concerns with regard to receiving unsolicited findings. In **Chapter 4** we describe the next step of our qualitative research, namely, analyzing the in-depth interviews using the constant comparative method to develop codes and themes. In the context of the return of unsolicited findings, four interrelated themes that cancer patients could experience emerged from our data.

To answer the second research question, a prospective, quantitative study among a large group of cancer patients was conducted. Participants completed a digital questionnaire based on the results described in Chapter 3. In **Chapter 5** we present the results of this study and describe quantitatively cancer patients' attitudes toward receiving unsolicited findings and sharing this information with family members. We also describe whether there are differences in certain patient subgroups.

The answer to the third research question is discussed in Chapters 6, 7 and 8.

Chapter 6 reports on disclosure dilemmas concerning family issues and describes some ethical challenges regarding the disclosure of genetic test results to family members. We discuss the question of whose duty it is to convey relevant genetic risk information concerning hereditary diseases that can be cured or prevented to the relatives of patients undergoing DNA sequencing. **Chapter 7** focuses on the question: should researchers and clinicians actively search for pathogenic mutations results now that whole genome sequencing is available? In other words: do healthcare professionals have a 'duty to hunt'? In **Chapter 8** we argue that patients do not have an obligation to receive genetic information. We recommend a disclosure policy that works with defaults and we strongly recommend that this disclosure policy should always be paired with an opt-out option. Finally, this thesis is concluded with a summary and general discussion in **Chapter 9** and a summary in Dutch in **Chapter 10**. In chapter 9 and 10, the results of the thesis are summarized, followed by general conclusions. We reflect on the ethical challenges of sequencing techniques and future perspectives are described.

Center for Personalized Cancer Treatment

Our study was conducted in close collaboration with the Center for Personalized Cancer Treatment (CPCT) and participants were recruited through the affiliated hospitals. In 2010, the three largest cancer centers in the Netherlands (the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, the Erasmus Medical Center Cancer Institute and the UMC Utrecht Cancer Center) decided to start working together on DNA-focused cancer research and founded the CPCT. Since the establishment of the CPCT, many hospitals have joined this initiative, including all academic hospitals and many non-academic hospitals in the Netherlands.

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Chapter 2

Unsolicited findings of Next Generation Sequencing for tumor analysis within a Dutch consortium: Clinical daily practice reconsidered

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Abstract

Cancer patients participating in studies involving experimental or diagnostic Next Generation Sequencing (NGS) procedures are confronted with the possibility of unsolicited findings. The Center for Personalized Cancer Treatment (CPCT), a Dutch consortium of cancer centers, is offering centralized large-scale NGS for the discovery of somatic tumor mutations with their germline DNA as reference. The CPCT aims to give all cancer patients with advanced disease stages access to tumor DNA analysis in order to improve selection for experimental therapy. In this paper our experiences at the CPCT will serve as an example to discuss the ethical and practical aspects regarding the management of unsolicited findings in personalized cancer research and treatment. Generic issues, relevant for all researchers in this field are discussed and illustrated by description of three patients faced with an unsolicited DNA finding, while they intended to be candidate for future anticancer treatment by participating in a trial that included NGS of both somatic and germline DNA.

As options for DNA analysis expand and costs decrease rapidly, more and more patients are offered large scale NGS testing.

After reviewing current recommendations in literature, we conclude that classical informed consent procedures need to be adapted to become more explicit in asking patients if they want to be informed about unsolicited findings and if so, what level of detail of genetic risk information exactly they want to be returned after the analysis.

Introduction

In the era of personalized cancer treatment, large scale genetic analysis of tumors is considered to be key for a better selection of patients for an appropriate anti-cancer therapy. Due to this development, cancer treatment is moving onwards from only organ based, one size fits all medicine, to specific anti-cancer treatments based on specific somatic genetic mutations.

With the rapid development of next-generation sequencing (NGS) it is now possible and affordable to sequence individual genomes in a short period of time to identify somatic genetic alterations[1].

Being a powerful diagnostic tool, the introduction of NGS is accompanied by ethical challenges. Since it is still important to sequence germline DNA as well as tumor DNA to identify true somatic tumor DNA mutations in an individual patient, one of these challenges is how to deal with genetic risk information that is inevitably generated by these tests and which may have potential medical, psychological, financial and social consequences[2]. These genetic findings are also challenging for laboratories performing whole genome sequencing, because many variants are not (yet) considered to be clinically relevant. Only a minority of variants is of direct clinical importance for patients and their family members[3].

In some cases the returning of genetic risk information after a NGS procedure is essential because of the possible impact and challenges for patients and their relatives. How this should be done is the subject of an ongoing debate. Like others [4,5], we are convinced that we have the responsibility to offer research participants the option to be notified of findings that potentially affect a person's health or may prevent significant harm.

The additional genetic information that is found in the search for better selection of anti-tumor treatment has many different annotations. Here we prefer the use of 'unsolicited' findings, because this describes that this finding was discovered unintentionally, as a by-product of a research question[6]. However, the terms ‘secondary’ findings or ‘incidental’ findings are also widely used.

The Center for Personalized Cancer Treatment (CPCT) is a Dutch consortium including the Netherlands Cancer Institute (NKI), 8 University Hospitals and over 10 large teaching hospitals in the Netherlands. The mission of this consortium is to improve treatment outcome and patient care in the field of oncology and avoid unnecessary exposure to side effects. In particular, the CPCT aims to give all cancer patients with advanced disease stages access to tumor and germline DNA analysis in order to improve selection for therapy. CPCT offers biopsies and sequencing in patients undergoing standard of care targeted treatment to generate a database. From 2011 until August 2015 , we have taken tumor biopsies and blood samples of over 600 late-stage cancer patients over the past three years and NGS has been performed in more than 370 tumor samples. The occurrence of unsolicited findings has proven to be not hypothetical, which was shown recently by findings in three patients that urged us to revisit the CPCT policy regarding disclosure of genetic risk information. In this paper our experiences at the CPCT will serve as an example to discuss the ethical and

practical aspects regarding the management of unsolicited findings in personalized cancer research and treatment. This may also guide other consortia when setting up NGS testing.

Next generation sequencing at the CPCT

The CPCT offers large scale NGS-based tumor diagnostics as of 2011. First, a comprehensive test for 'actionable' mutations based on the IonTorrent Personal Genome Machine (Life Technologies, Carlsbad, California, USA) and Illumina MiSeq (Illumina, Hayward, California, USA) has been adapted, which covers hotspot mutations in oncogenes and complete coding sequences of tumor suppressors but also allows for the detection of relevant copy number amplifications. This was offered as a diagnostic test. Secondly, we offered a so-called targeted mini-cancer genome sequencing panel, involving approximately 2,000 cancer-related genes. As sequencing output is increasing and running costs are decreasing, we have recently moved towards whole exome analysis. For correlation purposes to identify true somatic mutations, both tumor and germline DNA are sequenced on the same panels. In the near future, whole genome sequencing will be implemented.

Methods: Unsolicited findings and the CPCT disclosure policy

Patients that undergo tumor biopsies for NGS within the CPCT consortium all have advanced staged cancer. Our procedure is visualized in *figure 1*. Main selection criteria are: Age $\geq$ 18 year, locally advanced (irresectable) or metastatic cancer from a solid tumor, indication for systemic treatment with anti-cancer agents, evaluable disease (by for instance radiological imaging, physical examination and/or blood tumor marker), safe biopsy of a metastatic or locally advanced lesion possible, Expected adequacy to follow up and a written informed consent.

First, the treating medical oncologist will refer his or her patient to a CPCT investigator at the local institute. This CPCT investigator is a physician and preferably someone else than the patient's own medical doctor to reduce the therapeutic misconception, which occurs when someone misunderstands the distinction between the aims of a scientific study and clinical care[7]. Then the CPCT investigator informs the patient about the aims of the intended study, the study related procedures (including the biopsy procedure and blood draw to obtain tumor DNA as well as germline DNA) and the possibility of discovering unsolicited genetic findings. After the patient has had a reasonable time to consider participation in a NGS procedure, patients willing to participate sign informed consent. After written informed consent is obtained, the CPCT investigator subsequently initiates baseline screening to determine CPCT study enrollment. After definite trial inclusion, a blood sample and a biopsy from a metastatic lesion are taken, both as part of the CPCT study related procedures. Snap-frozen biopsy material and blood samples are transported to the central core facility at the department of Pathology at the University Medical Center Utrecht for centralized histological

assessment and DNA analysis. DNA sequencing and variant reporting is performed in the ISO15189-certified genome diagnostics lab of the Medical Genetics Department.

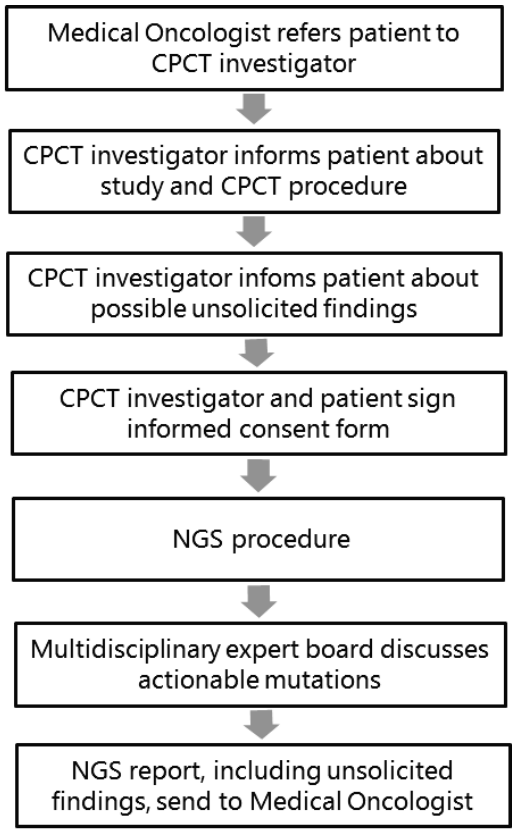

Figure 1.The CPCT NGS procedure

Reliable genetic variants are reviewed in a multidisciplinary team involving CPCT investigators, bioinformaticians, pathologists, medical oncologists, molecular geneticists and clinical geneticists to discuss possible actionable somatic mutations. This information is then reported back to the treating medical oncologist in order to inform their patients about potential treatment options. Patients with subsequent identified unsolicited findings are offered a referral to a clinical geneticist for further counseling and validation of the genetic variant in a second blood sample. This second blood sample is then analyzed in the DNA diagnostic laboratory of a Clinical Genetic Center.

Before 2014, if the patient consented to be informed about unsolicited findings which could lead to an increased risk of the development of cancer in their relatives, these (germline) findings were to be disclosed by their treating medical oncologist during a consultation. The policy of the research ethics committee (REC) regarding the return of research results

however has been to return clinically relevant and actionable unsolicited findings from studies, genetic findings included. Participants who do not want to receive these results were excluded from participation in order to prevent the researcher facing a serious dilemma when confronted with imaging findings or genetic risk information that may be of interest to the participant. Therefore we amended the study protocol and informed consent forms in 2014 in order to align to the REC policy.
Hence, an opt out option is no longer available. Patients that do not want their genetic risk information returned, currently have to decide either not to participate in the trial or to consent with receiving unsolicited findings. Currently, the suitability of this disclosure policy is under discussion, as the emergence of NGS has changed the circumstances under which many disclosure policies were designed[8].

Results

From January 2011 until August 2015, 3 out of 376 patients participating in CPCT trials were confronted with unsolicited findings derived from a NGS procedure of their tumor biopsies with matching germline blood samples. They participated in the NGS procedure with the hope that possible genetic information could be identified as a target for anticancer drugs which would allow specific treatment options. All three gave informed consent when an opt out on the return of unsolicited findings was available. Until August 2015, a total of 376 patients signed informed consent and underwent tumor biopsy. Table 1 shows the characteristics of 185 patients whose tumor biopsies are already sequenced.
The first patient with ovarian cancer participated in a CPCT study and underwent a tissue biopsy to retrieve tumor material and a blood draw for germline NGS testing. A germline BRCA2 1-bp deletion was reported. Patient had consented to be informed about possible unsolicited findings arising from the NGS procedure and was informed about the results by her medical oncologist. An appointment with a genetic counselor was made. The germline BRCA2 1-bp deletion was confirmed with a second specific and validated test in DNA extracted from a new blood sample. Patient 1 was relieved to hear the cause of her illness and immediately informed her family members and encouraged further investigations. She did so because she felt the urge to warn her relatives for the risks of breast and ovarian cancer. Recently, her daughter, who opted for predictive DNA testing and was diagnosed a mutation carrier too, has undergone prophylactic mastectomy to reduce her risk of breast cancer. At the time patient 1 was sequenced, in the Netherlands, screening for BRCA mutation was not routine for ovarian cancer patients. This patient was the first person in her family to be diagnosed with ovarian cancer; no family members with breast cancer were known and because of her age at diagnosis (above 60) she was not routinely referred for a diagnostic BRCA testing. Because this BRCA mutation would not have been detected if she had not participated in this study, we consider this an unsolicited finding.

Total patients sequenced at August 2015	***n= 185***
Age	63 (33-89) year
Gender	
Male	103 (55,7%)
Female	82 (44,3%)
Ten most common cancer diagnosis*	
Melanoma	31 (16,8%)
Colorectal	29 (15,7%)
Breast	23 (12,4%)
Sarcoma	9 (4,9%)
Liver	8 (4,3%)
Kidney	8 (4,3%)
Oesophageal	8 (4,3%)
Pancreatic	7 (3,8%)
CUP	7 (3,8%)
Lung	5 (2,7%)
Other cancer diagnosis	50 (27,0%)

* all patients are advanced staged cancer patients

Table 1. Patient characteristics

At this moment patient 1 has stable disease after her first line chemotherapy. Once disease progression occurs, she will be eligible for Poly (ADP-ribose) polymerase (PARP) inhibition. The second patient with metastatic breast cancer participated in screening for the CPCT phase 1 trials. A blood draw and tumor biopsy for NGS were subsequently performed. The NGS results showed a p16-Leiden mutation associated with Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome. The germline mutation was confirmed and patient was informed. We do not know if this patient has informed her relatives about the FAMMM syndrome, which is unrelated to the patient's breast cancer. This patient did not attend the appointment we arranged with our clinical geneticist. No further treatment options were available for this patient with an expected survival of just a few months. She interpreted the results as just another cancer related 'symptom' without feeling the necessity of further investigations or counseling. However, FAMMM syndrome may have serious consequences for family members, since this syndrome presents with life-threatening diseases, such as melanoma and pancreatic cancer. Patients carrying the p16-Leiden mutation qualify for regular surveillance to detect melanoma or pancreatic cancer at an early stage.
The third patient was diagnosed with a melanoma. He participated in a CPCT study to reveal whether he would be a candidate for future anticancer treatment with selective inhibitors of mutant BRAF V600E. A BRCA 2 missense mutation was discovered by NGS. Unfortunately,

patient died before genetic results were available. After validating this missense mutation, we could re-classify this missense mutation as a variant of unknown significance.

Discussion of current recommendations in the literature

Consensus now emerges that genetic risk information should be returned to patients[9] but disagreement exists what results should be communicated, how and by whom and to who. With the rapidly expanding use of NGS procedures generating large amounts of genetic data, informed consent procedures become increasingly important, but at the same time very challenging. Our recent experiences show that the return policy of unsolicited findings is of utmost importance to integrate in the NGS procedure. The question how, to who, by whom and which genetic risk information should be returned to patients is a very real one, which is expected to become more important. Our own experiences and discussions are reflected in ongoing international debates.

First, there has been an ongoing debate regarding the appropriate type of informed consent for NGS, including both the content and the procedure. Although the majority of experts state that the option to refuse genetic results should be addressed at the time of the informed consent, recently there are suggestions that patients should be able to reconsider their choices[10]. This means patients do not have to follow through on their earlier decisions. There is, in other words, a growing plea for facilitating the ongoing changing mind of participants during the study and after signing the informed consent form. This so-called '*dynamic consent*' provides additional functionality to allow on-going engagement and maintenance of research participants' consent preferences [10,11].

Overall the informed consent process and informed consent form should clarify the circumstances in which a patient might be re-contacted in the future. A topic for further debate is whether professionals should actively contact participants when new findings are found.

Second, there has been debate *how* patients should be informed. Several authors proposed to experiment with novel types of consent, among which tiered consent[2,12,13,14,15]. A tiered consent will give the participant a set of choices or well-defined packages *(see for example Table 2)* and allows the participant to choose, so it gives the patient greater control over the potentially available information [2,12,13].

These pre-defined options could consist for example of a default package and several optional packages[2,16]. The default package contains actionable information that is highly relevant for the patient, like directly life-saving information or information indicating serious health problems. The optional packages may include data of moderate clinical validity, or a package with reproductive information or data of 'personal or recreational' interest. In our consortium optional packages are not yet offered, but we currently perform an empirical ethics study to test the suitability of such a disclosure policy.

Category 1	**Category 2**	**Category 3**	**Category 4**
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.

Table 2. Four categories of possible NGS test results

Third, there has been debate what genetic information should be returned and how the family should be involved. The American Society of Clinical Oncology (ASCO) and the American Society of Human Genetics (ASHG) stimulate health care professionals to inform patients about the potential for genetic risks to their relatives. Also the CPCT, as well as other research groups are concerned with the question how this can be addressed appropriately. Our first patient encouraged her oncologist to further investigate her incidental finding, as she felt a responsibility for her family members.

Another family matter, postmortem disclosure of NGS results, should be taken into account as well, particularly in the context of cancer[17], as is sadly illustrated by our third case who died before genetic results were available.

Fourth, there has been debate *when* patients should be informed about the possibility of unsolicited findings. Within our consortium patients are informed beforehand about the possibility of unsolicited genetic risk information. Initially, they are briefly informed by their own medical doctor, and later by the CPCT investigator involved in the biopsy procedures. In other institutes, for example at the University of Michigan, all patients undergoing NGS procedure of their tumor had to meet with a genetic counselor before consenting to genomic analysis[18]. This might have been preferable in our second patient. She did not feel the necessity of further investigations or counseling concerning her unsolicited finding. Counseling by a genetic counselor in advance of her NGS procedure could possibly have altered her attitude towards receiving genetic information, so she could have opted out for results not directly associated with her current threatening diagnosis before the NGS procedure was performed. However, doing so in all patients eligible for NGS testing would

be a large burden for both patients and professionals, as the vast majority of cases will have no unsolicited findings at all.

Fifth, there has been debate whether patients should have the option to opt out from receiving genetic results. The American College of Medical Genetics and Genomics (ACMG) recommends a broader obligation to returning genetic information: they suggest a minimum list of 56 genes that should be routinely reported to the ordering clinician. In 2013, the ACMG recommended that these findings should be reported without asking upfront preferences from the patient and family and without considering the limitations associated with patient's age[19]. This ACMG policy statement sparked intensive discussions and was considered controversial because it could affect patients' autonomy and their potential interest in not knowing this genetic information. As a result, this policy statement is now withdrawn and the option to opt out is added. To opt out means that patients should have the option to refuse the return of genomic test results, both those related to the study purpose and those that are unsolicited findings, unless the study aims are related to the return of these data. Although we assume that the majority of patients are willing to receive not only the default package but also additional packages, which is confirmed in studies as well[20]**,** patients do not have an obligation to learn genetic information. Patients who are contacted regarding such results should have the right to decline receiving those results[21]. We earlier recommended to always allow an opt out for patients that participate in genome studies for receiving genetic information, also in case of unsolicited findings arising from the default package[8]. If an opt out was offered, our second patient had had the option to opt out for return of results except those relevant for her current breast cancer treatment.

Finally, we have to consider how family members should be involved. In our study this is highly relevant since we are dealing with patients with advanced malignancies with sometimes short life expectancies. This might result in difficult situations when one should decide whether and by whom the family members should be informed about discovered unsolicited findings, after the participant is deceased, which is particularly relevant for highly penetrant, dominant genetic mutations[17]. As a default, Boers et al propose a passive disclosure under at least three conditions. First, prior to the NGS procedure, patients should be counseled on the familial importance of genomic information and about possible postmortem disclosure to relatives. Second, an appropriate procedure for informing and counseling relatives should be agreed upon before implementing NGS. Last, there should be agreement on the selection of results, including those of immediate clinical significance, that are eligible for postmortem disclosure to relatives. Debate is necessary on whether and when active disclosure is more appropriate, and also by whom this should be done: family members or professionals[17]. Ormondroyd et al also describe a role for genetic counseling services, they concluded that genetic counselors should be involved instead of family members of deceased persons and inform relatives about genetic risk information[22].

Empirical research recently observed that patients who participate in trials are highly motivated to learn results and that there are numerous medically actionable results that could be derived from whole exome sequencing and whole genome sequencing[23,24,25]. Stimulating the development of educational materials that clearly communicate disease associations or the development of decision tools for patients and physician's is an open research field[14,26]. Further research is needed to compare different ways of disclosing results, also from patients' perspective and preferences in this field of rapid evolving NGS strategies in daily practice.

Conclusions and implications for clinical practice

Since NGS has become part of the current diagnostic armamentarium, there is a need to explicitly inform patients about possible unsolicited findings. The question how, to who, by whom and which genetic risk information should be returned to patients is a very real one, which is expected to grow due to the rapid developments in NGS. In our experience at least 1 percent of patients (3 out of 376) had unsolicited findings. These unsolicited findings have to be confirmed by a validated test and patients should be counseled by a genetic counselor. Informed consent procedures need to be more explicit in asking patients if they want to be informed about unsolicited findings and what genetic risk information exactly they want to be returned. For our CPCT consortium, and centers alike, a tiered informed consent, offering predefined packages can be used with options for patients to opt in and opt out for the return of unsolicited genetic results. More research, especially towards the needs and preferences of patients concerning the return of genetic risk information is needed.

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Chapter 3

Cancer patients' intentions towards receiving unsolicited genetic information obtained using next-generation sequencing.

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Abstract

Objective

Next-generation sequencing (NGS) can be used to generate information about a patient's tumour and personal genome. This powerful diagnostic tool provides solicited and unsolicited hereditary genetic (risk) information that could have consequences for cancer patients and their quality of life. A well-defined approach for returning appropriate genetic risk information is needed in personalized cancer care.

Methods

A qualitative design with semi-structured interviews was used. We conducted interviews with 24 Dutch patients with different types of cancer, both NGS-experienced and NGS-inexperienced, to learn their intentions, needs and preferences towards receiving unsolicited genetic information obtained using NGS.

Results

Almost all participants had a positive attitude towards receiving unsolicited findings. After receiving comprehensive background information on NGS, including a binning model of four categories of unsolicited findings, most participants preferred to receive only subsets of genetic information. Their main concern was their own and others'(including family members) ability to cope with (the increased risk of having) a genetic disorder.

Conclusion

Providing background information gave cancer patients the opportunity to select subsets of findings and increased their ability to make an informed choice. Special attention is needed for social and emotional factors to support the patients themselves and when communicating test results with their family members.

Introduction

Today, systemic cancer treatment decisions are based not only on the tissue of origin, but also increasingly on genetic information. Mapping the genetic sequence of tumours in individual patients is expected to become a central feature in personalized cancer care. Next-generation sequencing (NGS) technologies enable the affordable sequencing of whole genomes within a short timeframe. This powerful diagnostic tool can be used to generate solicited and unsolicited hereditary genetic (risk) information that could have medical, psychological, financial and social consequences for patients and a considerable impact on their quality of life.[1,2] A well-defined approach for returning genetic risk information to cancer patients and their family members is therefore needed.

We[3,4,5] and others[6,7] have developed disclosure policies for the feedback of genetic information in the context of large-scale genetic testing.[8,9] Some of these policies consist of tiered consent models, where genetic results are offered in categories of genetic mutations, also known as binning models.[1,2] Earlier empirical, often US-based, studies confirmed patients' and research participants' preferences to have results returned.[3,10,11,12,13,14] A few studies have specifically focused on cancer patients' preferences.[15,16,17,18] One of these tested a binning model, presenting six different types of individual genome sequencing results to a selected group of young breast cancer patients, who were found to be primarily interested in receiving information about actionable mutations.[16]

We earlier described the occurrence of unsolicited findings in a Dutch research setting.[19] Further research is needed to examine the preferences of cancer populations; therefore, we conducted interviews with 24 Dutch patients with different types of cancer, who included patients with or without previous NGS experience (NGS-experienced and NGS-inexperienced, respectively), to learn their intentions, needs and preferences towards receiving unsolicited genetic information obtained using NGS.

Methods

Design

A qualitative design using semi-structured interviews was used.

Participants

A total of 24 Dutch patients with different types of cancer, both NGS-experienced and NGS-inexperienced, were recruited by their oncologists. The main inclusion criteria were that they were 18 years old or older and had received a cancer diagnosis (any origin and any stage of disease). Patients unable to speak, read or write the Dutch language were excluded from the study.

Participants who had previously experienced a NGS procedure were informed by an investigator about the aims of that previous study, the related procedures, and also about the possibility of discovering unsolicited genetic findings.[19] After the patient had received a

reasonable period to consider study participation, those willing to participate signed an informed consent form, which included a paragraph addressing the possibility of discovering unsolicited findings. To complete the informed consent form, patients had to explicitly answer questions about whether they wanted to receive unsolicited findings.
We appoint these patients 'NGS-experienced', meaning that these participants intended to be candidate for future anticancer treatment by participating in a trial that included NGS of both somatic and germline DNA. Hence, the NGS-experienced participants already underwent a tumour biopsy for sequencing reasons and were familiar with the possibility of revealing unsolicited findings during the sequencing and also with the possible need for a referral to a clinical geneticist.

Semi-structured interviews
For the semi-structured interviews, an interview guide was developed and pre-tested. We adapted the surveys used in the ClinSeq study[11,20] and added questions concerning, for instance, perceived behavioural control and questions about patient needs and preferences regarding education and counseling when learning the results of NGS.
Our interview guide was based on the health-related theory of planned behaviour (TPB), following the guidelines of Ajzen.[21] This theory integrates a person's intentions to perform a specific behaviour, including their attitudes towards the behaviour, subjective norms, and perceived behavioural control. These intentions account for considerable variance in actual behaviour. The behaviour examined in this study was 'making a decision on receiving information about unsolicited findings from NGS'.
The research protocol was approved by the Research Ethics Committee (IRB) of the University Medical Center (UMC) Utrecht (The Netherlands), and written informed consent was obtained from all participants.

Interview procedure
Individual in-depth interviews took place at the UMC Utrecht Cancer Center. The interviews consisted of two parts and we showed patients two videos. The videos were used to ensure that all participants had received the same level of information on genome sequencing. *Figure 1* shows our interview strategy.
The videos were in Dutch and were developed by the authors. The first video provided each participant with the same background information about NGS procedures, for example why NGS is medically useful and to explain the possibility of generating unsolicited genetic information. After this video, we asked the participants for an initial response, particularly for their preferences on whether they would like to be informed about unsolicited findings. We also determined whether they had any concerns or additional remarks on this topic. *Figure 2* shows our semi-structured interview guide for part 1 of the interview.

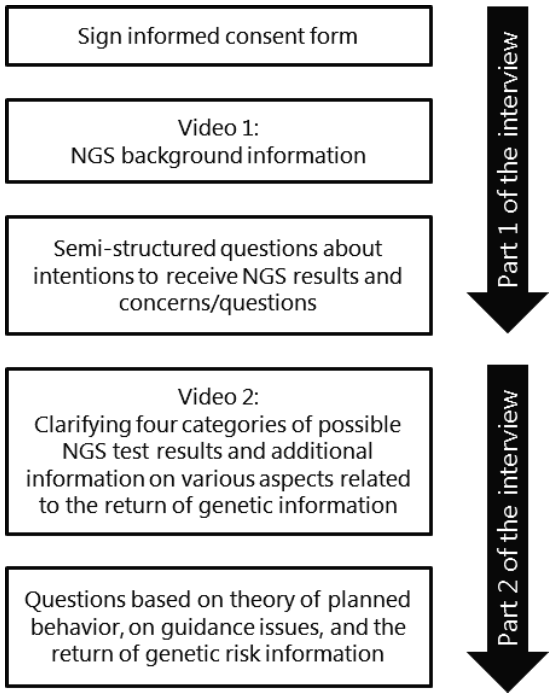

Figure 1. Interview strategy

In the second video, participants received information on various aspects related to the return of NGS results, as described in *Figure 3*. The investigators offered participants time to consider the information they had learned from the second video and asked all participants whether they had any questions.

Interview questions
- Would you like to be informed about unsolicited findings? Yes/No/other - What is the reason that you would or would not want to be informed about unsolicited findings? - What are reasons for having the intention to receive or not to receive information about unsolicited findings? - What do you see as advantage or disadvantage of being informed about unsolicited findings? - Are their persons in your vicinity who would approve your desire to be informed about the unsolicited findings? - Are their persons in your vicinity who would disapprove your desire to be informed about the unsolicited findings? - Are there any factors or circumstances that make it difficult or impossible for you to be informed about unexpected results? - What questions come to you when you think about this topic? - Are there any concerns when you think about this topic? - What additional information do you need, to make an informed decision about whether or not wanting to be informed about the unsolicited findings?

Figure 2.Semi-structured interview guide of part 1 of the interview

In the second video participants received neutrally worded, additional information on various aspects related to return of NGS results, including:
-type of results that might be generated
-information on prevention of a susceptible disease
-information on implications for family members
-information on psychological issues (like coping with test results and personal impact of disclosure)
-information on heredity
-impact on psychosocial issues (like personal and family relationships)
-impact of genetic testing on employment
-impact of genetic testing in insurance and mortgage
-information on data storage and privacy and confidentially

Figure 3.Topics discussed in video 2

They also learned about four distinct categories ("*bins*") of genetic information, shown in *Table 1*. These categories were based on our previously developed qualified disclosure policy.[3,4,11] In the second part of the interview, we used our binning model to present four distinct categories of genetic test results, asking questions based on TPB.[21]

Category 1	**Category 2**	**Category 3**	**Category 4**
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.

Table 1. Four categories of genetic test results

Data analysis

The interviews were audiotaped and transcribed verbatim. Data analysis was undertaken using the constant comparative method, which involves going back and forth from the data to develop codes, concepts and themes.[22,23] RB independently coded the full transcripts by labelling units of texts that referred to one or more topics relevant to the study's aim.

Coding was done with NVivo 10 software. HW and AB read the full coded transcripts and checked the codes for consistency. The codes were adjusted by comparison across transcripts and following discussion with the other authors. The coding outline was modified and transcripts were re-analysed.

Results

In total, 24 interviews were conducted between April 2014 and December 2014 by RB in the presence of HW, who made field notes during the interviews. Data saturation was reached after 21 interviews. In the last three interviews, it was confirmed that no new thematic content was found, and after interview 24 the recruitment was ended.[24] Each interview lasted approximately one hour. The interviews were conducted with seven participants with curable-stage disease and 17 with advanced-stage disease. From the advanced-stage cancer patient group, eight participants had previously had NGS performed on their tumours. All other patients were NGS inexperienced.

The majority of our participants were Caucasian. Participants were, on average, 60 years of age (29–79 years) and had a high level of education. *Table 2* shows the patient characteristics.

Attitude and intention

In line with the TPB, we invited cancer patients to think about their intentions towards receiving unsolicited genetic information. For our participants this was a hypothetical situation, as no real-life data were available to return to them. Most participants had a positive attitude towards receiving NGS results. At the start of the interviews, almost all participants, both curable- and advanced-stage, wanted to receive all available genetic information.

The intention to receive unsolicited findings changed during the interview. Initially, most participants indicated that they preferred to be informed about all possible genetic findings arising from NGS; however, after the second video, which introduced the four categories of genetic test results, more than half of our participants favored limiting feedback to one or more subsets of genetic variants.

Motivations for receiving unsolicited genetic information

When asked about their motivations for receiving unsolicited genetic findings, some of the NGS-experienced patients stated that they had participated in a sequencing procedure to contribute to the advancement of medical science in cancer treatment. These participants probably meant that they accepted the outcome of NGS as a package deal consisting of cancer-related personal treatment possibilities and possible unsolicited findings.

Patients (n = 24)	Total
Age 29-79 years	
≤ 55 years old	10 (42%)
>55 years old	14 (58%)
Gender	
Male	13 (54%)
Female	11 (46%)
Stage	
curative, NGS inexperienced	7 (29%)
advanced stage, NGS inexperienced	9 (38%)
advance stage, NGS experienced	8 (33%)
Educational level	
low	3 (13%)
medium	5 (21%)
high	16 (66%)
Diagnosis	
brain tumor	2
breast cancer	5
cholangiocarcinoma	1
colon carcinoma	1
epithelioid hemangio endothelioma	1
larynx carcinoma	1
melanoma	2
ovarian cancer	2
pancreatic cancer	1
prostate cancer	3
renal cell carcinoma	1
testicular cancer	4

Table 2. Patient characteristics

Interviewer: "Do you want to receive unsolicited findings?" Respondent: "Of course. I think medical science could develop more targeted tools" (Male, 52, advanced stage, NGS experienced). Another participant answered this question with: "Yes, for medical science" (Male, 78, advanced stage, NGS experienced).

Others stressed the importance of contributing to future healthcare from an economic point of view, by saving medication for those patients that would profit from a NGS-discovered mutation that could be targeted by anti-cancer treatment: "*The drug use and chemo*

treatments could perhaps then be even more specific" (Female, 67, advanced stage, NGS inexperienced) and "*The right resources in the right place*" (Male, 72, advanced stage, NGS experienced).

Most participants explicitly mentioned that they would like to receive unsolicited findings simply for their own interest: "*I did not need any motivation, I just did it for myself*" (Male, 72, advanced stage, NGS experienced).

Almost all participants, regardless of having curable- or advanced-staged cancer, indicated that they would be willing to adapt their lifestyle towards healthier behaviour or to undergo screening or (preventive) surgery to decrease their future disease risk. Our participants expressed their wish to be prepared for possible future diseases: "*So I can make some adjustments to my lifestyle (…) to prevent or to reduce the chance*" (Male, 37, curative stage, NGS inexperienced).

Some participants indicated that they would like to be informed about unsolicited findings to help their close family members, with some feeling responsibility towards their children: "*I would like to know if there are consequences (…), for me personally, especially for my children, and also for first- and second-degree family members, anything that they need to know*" (Female, 57, advanced stage, NGS inexperienced).

Conditions for receiving unsolicited findings

Regularly, participants spontaneously added conditions to be met before they would willingly receive unsolicited findings; for example, the condition only to receive unsolicited information if the disease would manifest itself in the short term. Participants wanted to be informed about conditions to which they were susceptible, the probability of developing them, expressed in percentages, the consequences of the disease and the availability of preventive measures: "*I would like to know more concretely which diseases we are talking about and what are their consequences (….),then I would like to know the likelihood of getting these diseases. I would then prefer to know (…) whether there is a possible form of prevention, or if something can be done with the knowledge, for example, making lifestyle adjustments*" (Female, 57, advanced stage, NGS inexperienced).

Several participants reported that they only wanted to receive information if there was an opportunity to influence the course of a susceptible disease: "*If you can do* something *to reduce the outcome of the disease, for yourself or the family*" (Female, 67, advanced stage, NGS inexperienced). "*If there is a high probability, for example 70%, that I could get Alzheimer's disease, then for me the information is of limited use*" (Male, 37, curative stage, NGS inexperienced).

Reasons why participants do not want to receive unsolicited findings

Although the majority of participants said they wanted to receive unsolicited findings, there were also some who were reluctant to receive this genetic information. The main reasons given were concerns about their own or others' ability to cope with a genetic disorder and the emotional burden they expect upon receiving this information. They also mentioned that they did not want to upset their family members: "*The downside is (…) that it can make you very depressed (…). I find it quite challenging to upset my children with particular information when it comes to genetic disorders*" (Female, 66, advanced stage, NGS inexperienced).
A few participants referred to insurance and privacy issues as reasons not to receive NGS results. Some participants stated they would like to remain ignorant of the possible return of their cancer in the future. "*I think it is very hard to explain to people who have not had cancer. It seems like something you just live with in your mind, but you would have known this for all these years*" (Female, 52, curative stage, NGS inexperienced).

Subjective norm

We asked patients whether specific individuals or groups in their personal lives would encourage or discourage them to receive unsolicited genetic findings. Almost all participants indicated that their family members and relatives would encourage them to receive the information. "*My wife, like my children, encouraged me*" (Male, 78, advanced staged, NGS experienced). A few participants stated that they did not care what other people recommended, and a few participants knew a relative would be reluctant to see them receiving unsolicited findings.

Perceived behavioural control

Cancer patients could be concerned about the barriers to making a decision to receive information about unsolicited NGS findings, particularly the anticipated emotional burden. These barriers involve the cancer patients themselves or their family members, particularly their children. In this context, they mentioned concerns about the heredity of their cancer: "*I immediately think about my children. I hope that they do not have the same genetic abnormality*" (Female, 69, advanced stage, NGS experienced).
Participants expressed concerns for the near future: "*The art of not knowing is that you have to deal with it very consciously (…). What is the consequence of knowing the unsolicited results and what is the consequence of not knowing?*" (Male, 52, advanced stage, NGS experienced).
Although participants discussed the impact on their families, almost all stated that the ultimate decision to receive unsolicited findings in the future is entirely up to themselves. One aspect facilitating the participants' ability to make a choice about whether to receive unsolicited findings was the possibility for them to adapt their lifestyle when an increased susceptibility to a specific disease was identified. The cancer patients considered the options

to undergo screening or (preventive) surgery to decrease their future disease risk, as described in 'Motivations for receiving unsolicited genetic information'.

Needs and preferences in education and counseling

To be able to make informed decisions, patients expressed several needs and preferences concerning education and counseling during the process of NGS.
Patients indicated their need to be supported when communicating the unsolicited genetic information to family members. "*How can I communicate the information to the people it concerns?*" (Male, 52, advanced stage, NGS experienced). Furthermore, patients expressed a need for written background information on the unsolicited finding: "(*I need*) *accessible, written information*" (Male, 74, advanced stage, NGS inexperienced), as well as the need of psychosocial assistance on demand: "*I wish that psychosocial support was offered, and that this support was still available even years later*" (Female, 57, advanced stage, NGS inexperienced).
Several participants asked for a period to decide whether they wanted to receive the unsolicited information: "*I can imagine a kind of 'waiting time', for example two weeks, to consider whether I really want these results*" (Female, 52, curative stage, NGS inexperienced). Another participant would like to involve his family doctor, by giving him a sealed envelope that at some point in time could be opened to share the unsolicited information (Male, 37, curative stage, NGS inexperienced).

Discussion

The behaviour examined in this study using TPB[21] was 'making a decision on receiving information about unsolicited findings from NGS'. Consistent with the literature,[3,10,11,13] the attitude of most of our participants, both curable- and advanced-stage, NGS-experienced and NGS-inexperienced cancer patients, was positive towards receiving (unsolicited) genetic information from NGS performed during cancer diagnosis. After more background information on the NGS procedure and the various aspects related to returning the results was provided, including the four categories of unsolicited findings, our participants became more conservative and seemed to be more aware of the possible consequences of receiving genetic risk information. They adjusted their answers to receive only subsets of information instead of all genetic variations. This is in line with findings of Bollinger et al.[12], who showed that patients change their preferences regarding the disclosure of unsolicited findings after discussing different types of results. Other quantitative studies in cancer patients[25] and healthy persons[26] have also confirmed that study participants provide more nuanced answers when given more background information. This underscores the importance of providing adequate information and counseling. Receiving (written) information was previously described as a tool to reduce patients' anxiety,[27] and as being reassuring.[28] Written information facilitates better understanding and decision making and can also help

patients to communicate genetic information to their families.[29] Receiving unsolicited findings in person, from a medical professional or genetic counsellor or geneticist, could help to explain the results and their implications.[15,16]

Participants in our study expressed clear conditions for receiving unsolicited findings, such as information about the probability of developing a particular condition (expressed in percentages) and the availability of preventive measures for the diseases that could be revealed.

The patients showed interest in gaining knowledge about their health and body, as well as information on how to prevent future diseases. They suggested that receiving genetic insights would give them the opportunity to prepare their personal lives and, if necessary, make health-related lifestyle adjustments. Although they discussed their personal social environment in detail, patients declared that the final decision to receive unsolicited risk information was completely their own. This question was explicitly asked to every participant for all four categories of results (outlined in *Table 1*). For each category, almost every patient indicated that they wanted to make the ultimate decision on receiving information by themselves. This subjective norm result is notable and worthy of further investigation, given the inherent familial nature of genetic results.

In order to understand how the grouping of genetic information into multiple categories may support patients to sustain or improve their health, we will use the concept of health as introduced by Huber et al. in 2011: "Health as the ability to adapt and to self-manage, in the face of mental, social and physical challenges".[30] This concept describes health not as a stable endpoint, as in the traditional WHO definition, but highlights function, resilience and self-direction. This definition is useful in this context for several reasons. First, it focusses on the patient's capability to cope with health conditions rather than on the actual impairments. In our study, participants changed their preferences after they encountered the possibility of receiving categories of genetic information; moreover, patients valued the opportunity to choose between packages. Applied to this definition, distinguishing between categories of diseases gives patients the opportunity to select a subset of findings, which might increase their ability to deal with unsolicited genetic information. Clinically actionable findings might enable these patients to lead a healthier life and consider themselves as healthy, while other findings (e.g. incurable diseases) emphasize their inabilities and therefore make them feel ill. Second, Huber and colleagues acknowledge the importance of social factors as constitutive features of health. We have shown, using the TPB, that the attitudes of family members, doctors and other important persons influence the patients' intentions towards receiving genetic findings. Third, the finding that perceived behavioural control influences the way patients perceive genetic information also fits within Huber's definition. Anticipated psychological stress, either their own or in relatives, changes patient perspective on the feedback of unsolicited findings.

Study limitations

Our study has some limitations. Most participants were Caucasian, highly educated, and all were recruited from a single (though large) Dutch academic hospital; therefore, the results may not be generalized to other patient populations. Further, our participants might have been particularly interested in DNA sequencing or might be familiar with NGS procedures, for example due to previous procedures. In addition, the feedback of unsolicited findings was presented as a hypothetical situation, as none of the participants with NGS experience had received an unsolicited finding.

Despite offering information as comprehensibly as possible, it became clear during the interviews and the subsequent analysis that this is a complex topic, and that some participants had difficulties differentiating between the aims of a NGS procedure and the research question concerning the return of unsolicited findings.

Comparing participants that had actually undergone NGS with those who were NGS inexperienced could provide interesting insights, as could the comparison between curative- and advanced-stage cancer patients, or determining the differences between younger patients of childbearing age versus older patients. However, a qualitative study typically has a relatively small sample size which means that we were not able to generalize the results of our semi-structured interviews into different subgroups of participants. More quantitative research is needed to examine the feedback of unsolicited findings in larger groups to better explore differences between these patients. Based on our qualitative study, we are now setting up quantitative research that will focus on a larger group of cancer patients.

Clinical implications for daily practice

During the use of NGS in clinical practice, education and counseling is vital to enable patients to make an informed choice. Presenting categories of genetic test results was found to be a useful tool in enabling cancer patients to make a well-informed decision about receiving unsolicited findings from NGS. Like other patient groups, our cancer patients adjusted their answers after receiving more background information. They seemed to be more aware of the possible consequences and choose to receive only subsets of information instead of all genetic variations linked to disease.

Special attention must be given to the social and emotional factors needed to support the patients themselves as well as their communication of the test results with their family members. Also, an important point for healthcare professionals to acknowledge is the fact that this topic is rather difficult to understand, even for highly educated patients.

The results of our study emphasize the importance of providing tailored information related to the return of NGS information. We highlight the importance of supporting healthcare professionals in the education and counseling of patients when communicating unsolicited results in the context of personalized cancer care and NGS. A decision aid should be developed to optimally support cancer patients.

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Chapter 4

Managing unsolicited findings in genomics: a qualitative interview study with cancer patients

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Abstract

Objective

Next-generation sequencing (NGS) is increasingly being employed in the context of personalized cancer treatment. Anticipating unsolicited findings that may arise during a NGS procedure is a key consideration; however, little is known about cancer patients' intentions, needs, and preferences concerning the return of unsolicited findings.

Methods

A qualitative design using individual semi-structured interviews with 24 cancer patients was utilized to explore patients' decisions on whether to receive unsolicited findings from NGS. These interviews were subsequently analyzed using the constant comparative method to develop codes and themes.

Results

We identified four interrelated themes that emerged in the context of the return of unsolicited findings. First, we describe how cancer patients expressed a strong need to control their lives. Second, we show the importance of family dynamics. Third, the NGS procedure regarding unsolicited findings is perceived as cognitively complex, and fourth, the procedure is also considered emotionally complex.

Conclusions

The results of our study contribute to a better understanding of what cancer patients consider important and what may motivate and influence them when making decisions on the disclosure of unsolicited findings following NGS. We show how Joel Feinberg's classification of autonomy may help clinicians to better understand cancer patients' desire for autonomous decision making while also acknowledging the emotional and cognitive difficulties regarding the disclosure of unsolicited findings.These insights could be helpful for clinicians to guide patients through this complex process.

Introduction

Next-generation sequencing (NGS) technologies enable the sequencing of whole genomes in a short period of time. Instead of the former one-size-fits-all organ-based medicine, modern personalized cancer treatments match patients to treatments most likely to be effective or prevent patients from exposure to unnecessary medications and subsequent side effects.[1]

NGS has become the method of choice in research laboratories, for example to determine the mutational load to assess eligibility for therapy strategies and to detect actionable driver mutations that are potential therapeutic targets.[2] Hence, genomic testing has enormous potential in oncological research and is also increasingly being used to treat cancer patients. Cancer is a disease of various somatic mutations in a huge number of genes that are not inheritable. Sequencing procedures generate large amounts of data and carry the inherent potential to generate unsolicited genetic (risk) information as both tumour and germline DNA are sequenced. These amounts of data need to be further investigated to see if a mutation is a pathogenic abnormality (and not a Variant of Unknown Significance or benign variant). These unsolicited findings could have considerable impact on patients' lives due to potential medical, psychological, financial and social consequences. In addition, these findings may have impact on patients' relatives. Despite the fact that unsolicited findings are rare, the increased use of sequencing procedures in daily practice means that more and more cancer patients are involved in DNA sequencing and might face unsolicited findings.[3] It is therefore important to be informed about cancer patients' opinions towards unsolicited findings and to provide patients and health workers with knowledge about genomics and the consequences of a NGS procedure.

In the Netherlands, NGS is offered to adult cancer patients by the Center for Personalized Cancer Treatment (CPCT), a Dutch consortium of cancer centers. Patients whose (somatic) NGS test results reveal unsolicited findings are informed by their oncologist and offered a referral to a clinical geneticist for further counseling and validation of the genetic variant in a diagnostic laboratory of a Clinical Genetics Center.[4] Returning these unsolicited findings raises challenges for patients and their family members. Several studies have shown that patients are generally positive about receiving unsolicited findings.[5–9] This also holds true for cancer patients,[10-13] but research suggests that patients become more cautious to receive all types of risk information when they are informed about the potential consequences for themselves and their family members.[14] The possibility of encountering unsolicited findings makes clinical decision making in oncology even more complex, and a thoughtful disclosure policy is needed. To support clinicians and patients who are confronted with these decisions, it is crucial to elucidate cancer patients' intentions, needs, and preferences in making decisions concerning the return of unsolicited findings. We earlier published a qualitative study[14] using semi-structured interviews with cancer patients to learn their intentions, needs and preferences towards receiving unsolicited findings generated by NGS. In this paper, we further explore their decisions about whether or not to receive unsolicited findings from NGS

and their corresponding concerns. We first describe four interrelated themes that emerged from our semi-structured interviews. We subsequently show how Joel Feinberg's classification of autonomy[15] may help clinicians to better understand cancer patients' desire for autonomous decision making while also acknowledging the emotional and cognitive difficulties regarding the disclosure of unsolicited findings.

Methods

Participants and data analysis

As described earlier,[14] a total of 24 participants were recruited at the University Medical Center (UMC) Utrecht, a total of eight oncologists were involved. Patients' oncologist briefly introduced this qualitative study during a regular visit to the UMC Utrecht outpatient Oncology clinic. The oncologist asked permission for investigator RB to contact them and provided an information brochure. RB gave more background information on the purpose and content of the study. During the interviews, all participants were provided with the same (videotaped) background information.[14] The main inclusion criteria for this study were: patients were 18 years of age or older and had received a cancer diagnosis (any origin and any stage of disease, hereditary condition or not). Patients who were not able to speak, read, or write the Dutch language were excluded from the study.

We distinguished between 'NGS-experienced' and 'NGS-inexperienced' patients, based on whether participants were part of a trial that included a combination of somatic and germline sequencing. Hence, the NGS-experienced participants already underwent a tumour biopsy for sequencing reasons and were previously informed about the possibility that unsolicited findings could be revealed. *Table 1* shows the patient characteristics of the participants.

During the interviews, the participants were asked about their intentions, needs, and preferences towards receiving unsolicited genetic information obtained using NGS. These unsolicited findings were explained to them as findings that could be discovered unintentionally, as a by-product of a research question. The semi-structured interview guide was based on, amongst other aspects, the health-related theory of planned behavior (TPB), which was also used in the Clinseq study.[6,16] This theory links intentions to perform behavior with attitudes toward the behavior, subjective norms, and perceived behavioral control; and these intentions, together with perceptions of behavioral control, account for considerable variance in actual behavior.[16]

The interviews were conducted in UMC Utrecht between April and December 2014, until data saturation was reached.[17] The research protocol was approved by the UMC Utrecht Research Ethics Committee (IRB) and written informed consent was obtained from all participants. The interviews were analyzed using the constant comparative method. The authors (RB and HW) went back and forth between the data and developed codes. The codes were categorized and adjusted by comparison (RB, RW, HW, AM, and AB). During a discussion with the other authors, the concepts and themes were conceptualized and

identified,[18,19] and finally, we reflected our findings in light of Feinberg's classification of autonomy.[15]

Patients (n = 24)	**Total**
Age 29–79 years	
≤ 55 years old	10 (42%)
>55 years old	14 (58%)
Gender	
Male	13 (54%)
Female	11 (46%)
Cancer stage	
curative, NGS-inexperienced	7 (29%)
advanced, NGS-inexperienced	9 (38%)
advanced, NGS-experienced	8 (33%)
Education level	
Low	3 (13%)
Medium	5 (21%)
High	16 (66%)
Diagnosis	
Brain tumor	2
Breast cancer	5
Cholangiocarcinoma	1
Colon carcinoma	1
Epithelioid hemangio endothelioma	1
Larynx carcinoma	1
Melanoma	2
Ovarian cancer	2
Pancreatic cancer	1
Prostate cancer	3
Renal cell carcinoma	1
Testicular cancer	4

Table 1.Patient characteristics

Results

When exploring cancer patients' intentions, needs, and preferences towards receiving unsolicited genetic information obtained by NGS, we identified four interrelated themes that emerged from our semi-structured interviews. We focused on these themes to elaborate more insight in patients' considerations and thoughts when managing (information on) unsolicited findings.

We here describe the four themes, illustrated with citations of our participants.

First theme: cancer patients' need to control their lives

During the interviews, the participants showed interest in gaining knowledge about their health and body, as well as information on how to prevent future diseases. In particular, participants suggested that having insight into unsolicited genetic information would give them the opportunity to be prepared for risks in their personal lives. "Then you can possibly make lifestyle adjustments, for example concerning diet or other preventive measures, if you know what to expect." (Male, 75, advanced stage cancer, NGS-experienced). If necessary, they would make health-related adjustments to their lifestyle and undergo regular examinations or preventive interventions. "The main reason is that I think and believe you can prevent diseases through adaptations in your diet or lifestyle or whatever." (Male, 67, advanced stage, NGS-inexperienced).

If an increased risk of a hereditary disease was detected, patients also mentioned the option to not have children. "If something in my genes were not correct, then I wouldn't have children." (Male, 74, advanced stage, NGS-inexperienced).

Patients frequently mentioned that being aware of unsolicited findings would give them the opportunity to prepare for the future, both emotionally and practically. Practical affairs that were suggested included making home adaptations and arranging financial matters. The patients said that insights from unsolicited findings would affect quality-of-life decisions and could be helpful in designing their lives. "It could help me to organize the rest of my life." (Female, 44, advanced stage, NGS-inexperienced).

Patients identified the potential impact of these findings on their lives as a criterion to decide whether to receive unsolicited findings. While for some this constituted a reason to want this information, others perceived it as a reason to reject disclosure. "If it's something serious, something that strongly affects your life, then I don't want to be informed." (Female, 66, advanced stage, NGS-inexperienced).

Patients suggested that they would like the possibility of adjusting their informed consent in the future; for example, at the moment that a currently untreatable disease (such as Alzheimer's disease) becomes treatable. "Because I am confident that [untreatable diseases] will be treated in the future." (Female, 67, advanced stage, NGS-inexperienced).

In summary, the patients expressed a need to control their lives, which seems an important influencing factor in making decisions concerning the disclosure of unsolicited findings from genetic tests.

Second theme: Cancer patients' involvement in family dynamics

Participants were concerned about their family members in several ways. They felt responsibility in making decisions regarding unsolicited findings that may affect their relatives.

The majority of participating patients mentioned that the potential benefit for family members, their children in particular, is a major motivation to learn about unsolicited findings. Patients indicated, often without being explicitly asked about it, that they considered their family members when thinking about making the decision to receive feedback on unsolicited findings. *"I already have cancer […]. Suppose I get Alzheimer's. It is questionable, because of my cancer diagnosis, whether I will ever reach that moment, but for my child and grandchildren, I really would like to know."* (Female, 64, advanced stage, NGS-experienced).

We found that patients were willing to consult relatives on whether to receive unsolicited findings. Often, they mentioned that they would discuss this topic with their children and/or their siblings before making the decision. *"Of course, I have discussed with my children as much as possible, whether they want to know."* (Male, 75, advanced stage, NGS-experienced).

In general, patients indicated that they would expect to be encouraged by most family members to receive feedback on unsolicited findings or that they expected that family members have a positive attitude towards receiving such information. This was equally true for siblings as for children.

Patients were worried about how to share genetic information with family members and were concerned about the anticipated burden that this knowledge would place on relatives, particularly by sharing information on hereditary diseases. Sometimes, they brought this up as a reason not to inform them about such conditions. *"The worry is about your family. It is quite something to burden your children with particular information that concerns hereditary conditions."* (Female, 57, advanced stage, NGS-inexperienced).

Several patients mentioned at least one family member who probably would not want to know that they are at risk for a genetic disease; for example, because they prefer a life without knowledge of a genetic threat. Moreover, some family members would probably not want to receive unsolicited findings because they were old, and the expected personal benefit was therefore low. When asked, some patients indicated that certain family members probably would discourage the patient from receiving the unsolicited findings , or would not support them to do so.

In short, during NGS procedures and making the decision to receive unsolicited findings, cancer patients are likely to closely involve their family members and also take into account the interest of these relatives in receiving genetic risk information.

Third theme: Cognitive complexity of NGS procedures

During the interviews, participants demonstrated that dealing with the return of unsolicited findings is complex on multiple levels. Although all participants were provided with the same information leaflet and watched the same background videos, most respondents showed difficulties in cognitively processing information about sequencing procedures; thus, we found that it was difficult for patients to achieve sufficient knowledge and understanding of NGS procedures. Fatigue and concentration difficulties can also be of influence, but this is

not necessarily problematic as this represents the real-world predicaments of cancer patients. During the interviews we allowed a short pause, to allow patients to recover. Although it took time and effort, most participants eventually seemed to comprehend the information. However, some misconceptions were still expressed, like *"DNA, does that have something to do with the family?"* (Female, 79, advanced stage, NGS-experienced).
Participants found it sometimes difficult to maintain focus on the research question concerning their decision about the return of unsolicited findings and the overall possibilities resulting from undergoing a NGS procedure. The researchers were frequently asked to reiterate questions, and in addition, participants explicitly stated that questions were difficult to answer. "*These are really tough questions.*" (Male, 74, advanced stage, NGS inexperienced).
Despite offering information comprehensive information and the fact that more than half of our participants were highly educated, the investigators repeatedly observed that the topic of NGS was complicated. "*Very difficult, I find it very difficult. I don't need all those unsolicited findings at all.*" (Female, 79, advanced stage, NGS-experienced).
Participants had difficulties differentiating between the primary aim of the NGS procedures (elucidating potential targets for cancer treatment) and the return of unsolicited findings. In summary, patients perceive NGS procedures and decisions about the return of unsolicited findings as highly cognitively complex. Despite the fact that our participants were relatively highly educated, the information was not easy to convey.

Theme 4: Emotional complexity of NGS procedures

Our participants also anticipated experiencing an emotional burden after the disclosure of unsolicited risk information. They struggled to reconcile their wish to be informed with their desire to have an open and untroubled future. "*My primary reaction is simply: No, I have had breast cancer and I don't need to know if I ever have the chance of getting, for example, colon cancer.*" (Female, 52, curative stage, NGS-inexperienced). Participants explained their anticipation of distress upon losing an open perspective of the future using hypothetical examples: "*For example, if I know I am about to get Alzheimer's disease, the first time I forgot my neighbor's birthday, I would think: oh no, Alzheimer's is beginning already. No, for me this would just cause extra stress.*" (Male, 67, advanced stage, NGS-inexperienced).
During the interviews, participants worried about the emotional consequences for themselves "*The disadvantage is, of course, that if it [the unsolicited finding] is a serious, life-threatening or life-altering disease […], it could make you very depressed.*" (Female, 66, advanced stage, NGS-inexperienced).
Subsequently, they were concerned for others, such as their family members. Some patients expected to face emotional difficulties in sharing genetic aberrations with family members. They would be afraid to tell their relatives, particularly their children, possible bad news. "*I am afraid to share certain knowledge with my children when it comes to genetic disorders.*" (Female, 57, advanced stage, NGS-inexperienced).

Patients also seemed to be aware of the possible emotional impact of returning unsolicited findings for vulnerable patients "*I would like to mention that I could handle unsolicited findings well, but I might also suggest that for people who have mental health problems or are more easily upset, this kind of information should not be shared.*" (Male, 29, curative stage, NGS-inexperienced).

In summary, patients perceive decisions on unsolicited findings as emotionally complex, stating difficulties regarding the impact for themselves, their relatives, and vulnerable patients.

Discussion

During the last few years, the issue of unsolicited findings has been discussed and reviewed regularly in the literature.[20,21] However, little is known about cancer patients and their intentions, needs and preferences concerning the return of unsolicited findings. Besides this, there are several reasons to assume that we cannot extrapolate the results of other patient groups or the general population to cancer patients. For example, sequencing of a cancer patients' tumour is linked with possible treatment options, instead of using sequencing mainly as a diagnostic instrument as in clinical genetics.

In our current study, we focus on the themes that emerged during semi-structured interviews with cancer patients and we reflect on our findings in light of Feinberg's classification of autonomy. Four interrelated themes were recognized when cancer patients were asked about their preferences, intentions, and needs concerning the return of unsolicited findings generated during a NGS procedure: cancer patients' need to control their lives (theme 1), associated family dynamics (theme 2), and dealing with both the cognitive complexity (theme 3) and emotional complexity (theme 4) of receiving the findings.

Despite the fact that all participants have to cope with cancer, their answers showed that they want to maintain control in other aspects of their lives. No matter how intricate these decisions on receiving genetic testing results may be, participants suggested that they would want to be the authors of this particular chapter of their life. Patients indicated that they would have the ultimate decisional authority.

Cancer patients found the return of unsolicited findings to be a cognitively complex process; even for patients with a relatively high level of education, it was difficult to grasp concepts such as DNA, heredity, and penetrance, and it was even more challenging to see how this might affect their personal situation. This finding is consistent with other studies that show that an adequate understanding of genomic testing requires a high level of genetic literacy that is difficult to obtain.[22,23] These obstacles are not entirely specific to NGS, as they are present in targeted genetic tests as well; nevertheless, the range of information that whole exome/genome sequencing may produce makes cognitive processing even more demanding.

Another issue we identified in our study is emotional complexity, which operates on multiple levels. Facing the prospect of future disease, alongside the inherent uncertainty as to whether this disease will ever reveal itself, can be distressingly burdensome. For cancer patients, who are already confronted with a life-threatening disease, this information constitutes yet another predicament. In addition, this information could affect family members, and the need to share it seemed like a daunting task for patients who are already sick.

The way self-control is articulated in this article may seem paradoxical, particularly because autonomous decision making seems challenging in light of the cognitive and emotional constraints and even more complicated by the potentially conflicting interests of their relatives. However, these findings are not necessarily contradictory. Many previous contributions to the debate on genomics have pointed out that autonomy should not be taken to imply that individuals are isolated moral beings that are blind to social circumstances and the needs of others.[24,25] In addition, autonomy is not singular concept in ethics.[26] Rather, it is a heap of related yet distinctive meanings, which could refer to different capacities, virtues, ideals and rights.[15] We use Joel Feinberg's classification of autonomy to interpret our findings and to explain why the need for control is not necessarily at odds with the other themes.[15] Failure to discern between these different connotations may lead to mutual misunderstandings between doctors and patients, and subsequently to unjustified conclusions. By using Feinberg's classification of autonomy to exemplify the different dimensions of autonomy that can be recognized in how patients talk about unsolicited findings, we aim to help clinicians to better understand cancer patients' preferences. Hence, this classification encourages clinicians to unravel the different messages that they intend to bring across by speaking about autonomy and control.

First, autonomy could be defined as a threshold above which patients have the *capacity* to make decisions; for example, concerning the return of unsolicited findings. Autonomous decision making on the return of unsolicited findings, albeit important, may sometimes be beyond the physical and emotional abilities of severely diseased patients. In these situations, healthcare professionals may sometimes be compelled to make decisions that are considered to be in the best interests of the patient. Even a patient who possesses the capacity to self-govern can be faced with circumstances that hamper the use of their autonomous capacities.

However, our study showed that patients struggle with the cognitive processing of information about unsolicited findings and lack a robust knowledge of NGS.

Next to this cognitive complexity, emotional distress, not uncommon in cancer patients, may also impact a patient's decisions. It does not follow, however, that patients should not have the ability to choose which results they would like to receive. Many participants in our study were highly educated and perfectly able to make a variety of decisions in live, both inside and outside health care. To conclude that those patients do not meet the threshold for autonomy as a capacity would be a preposterous claim. Instead, autonomy as a capacity

(mere competence) has to be distinguished from autonomy as an actual condition, which is a second dimension of autonomy. Even a patient who normally possesses the capacity to self-govern can be faced with circumstances that hamper the deployment of these autonomous capacities. Therefore, favorable circumstances should be shaped for cancer patients to be able to act autonomously. Vital conditions when dealing with the complexity of unsolicited findings include no time pressure, education and personalized guidance, and counseling, for example supported by decision aids.[27]

Obviously, the starting point should always be a good relationship between patient and physician, based on trust, transparency, partnership, and (paying) attention to the patients' values and preferences.[27,28] The longstanding emphasis on good counseling in the field of clinical genetics is not a trivial concern that can be waived when genetic testing becomes more widely used by non-genetic specialists (a trend referred to as mainstreaming). Rather, oncologists should take full advantage of the tremendous experience in the field of genetic counseling.

Third, autonomy could be referred to as a moral ideal. Feinberg describes a set of virtues that are used to describe autonomy as an actual condition, but also constitute, if present in the right degree, an ideal that human beings should strive for.[15] These virtues include self-determination, distinct self-identity, self-generation, and responsibility for oneself. These distinct aspects of autonomy can clearly be recognized in the results of our study: patients identify these traits as components of an ideal that is worth striving for. During the interviews, almost all cancer patients expressed their wish to make decisions on the return of unsolicited findings on their own (self-determination). Although family members are frequently consulted for advice, it was emphasized that patients felt that the ultimate decision was theirs to make (distinct self-identity). Moreover, unsolicited findings were perceived as useful information to shape and adapt their future life plans (self-generation), thus to take responsibility for their own course of life (responsibility for oneself). Healthcare professionals may not only acknowledge these traits of autonomy in their patients, but could also foster patient autonomy as a valuable ideal. Patient empowerment and shared decision making are familiar terms in genomics; however, if healthcare professionals do not want these ideals to become buzzwords, they should not only check a list of formal criteria, but also ask how patients and their family members can genuinely be supported in making decisions aligned with their actual preferences. Notably, the opportunity to engage in decision making constitutes the ideal, but this ideal does not entail a duty incumbent on all patients to act autonomously, regardless of their personal circumstances.[29] Nor does acknowledgement of autonomy as an ideal amount to the conclusion that everything should be provided whatever a patient asks for, regardless of costs, time, risks, etcetera.

Finally, autonomy is seen as a personal right. Autonomous decision making as a patient right, described by Feinberg as legal autonomy, is a longstanding tradition in bioethics and healthcare law. In genomics, the right to know as well as the right not to know are well-established specifications of autonomy as a patient right.[30,31] Some authors have advanced

the claim that the benefits associated with receiving unsolicited findings outweigh this right to respect autonomy. Previously, we have argued that respect for patient autonomy requires at least the option to opt-out from receiving unsolicited NGS findings.[32,33] Our study provides empirical support for this view, as it shows that clearly affirm their needs and preferences in deciding which results should or should not be disclosed. Furthermore, the finding that several patients had at least one family member who they expect would not want to be informed about genetic results stresses the importance of protecting the autonomy (in this case embodied in the right not to know) of family members too. Not offering a possibility to opt-out neglects such rights, which could severely disrupt physician-patient relationships. This may well be counterproductive, since many patients are very eager to receive at-least actionable findings. This is consistent with other qualitative and quantitative studies that show that an overwhelming majority of patients would opt to know these results.[20] Thus, an opt-out is vital to ensure that patients feel respected but will hardly be used in practice.

In conclusion, the results of our study contribute to a better understanding of what cancer patients consider important, and what motivates and influences them when they make decisions on the disclosure of unsolicited findings. These insights, combined with a theoretical framework that explains the various understandings of the concept of autonomy, might constitute a valuable background for clinicians to guide their patients through the exciting, but also challenging, field of genomic-driven oncology and shared decision making.

Study limitations

Our study has some limitations. Most participants were Caucasian, highly educated, and all were recruited from a single (though large) Dutch university hospital, possibly impeding the generalization of findings to other cancer patient populations.

Despite all the measures to facilitate understanding, including the use of carefully pre-tested questions, a short break during the interviews and both written and videotaped background information, NGS remains a difficult topic for patients to understand. In addition, there might have been some self-selection, as the patients who participated in our study might have been particularly interested in or familiar with NGS. Subgroup analyses were not possible due to the small sample size, which is common in qualitative research.

Further research is needed to elucidate differences between certain subgroups, e.g. patients with curative and advanced disease, people with and without a hereditary type of cancer, men and women, and young and older patients, and to develop evidence-based decision-making tools for patients dealing with unsolicited findings.

Clinical implications

Cancer patients may be particularly vulnerable (physical and emotional) at the moment they have to make decisions concerning NGS and possible unsolicited findings. Understanding

what a cancer patient could experience during the process of disclosing unsolicited findings from NGS will help oncologists in daily practice to accompany patients in making informed decisions. In Supplement 1 Table 2 we summarize our findings and practical implications of four dimensions of autonomy, according to Feinberg;[15] for example, in dealing with the several layers of complexity of a sequencing procedure, conditions such as no time pressure for decisions, education, personalized counseling, and guidance are vital. Cancer patients can be supported with family dynamics by assisting their communication with family members and offering guidance when dealing with stressful results.

Dimensions of autonomy	Our findings	Practical implications
Autonomy as a capacity to make decisions	▪ In general, patients have the capacity to make treatment decisions regarding the return of NGS results[#].	Healthcare professionals consider a patient competent unless compelling reasons exist to question this presumption.
Autonomy as an actual condition	▪ Due to the emotional complexity or acute or severe illness, it is particularly challenging for patients to grasp how the return of unsolicited findings might affect their personal situation and the situation of their family members. ▪ Even highly educated patients struggle with the cognitive processing of genetic information and lack a robust knowledge of NGS (i.e., cognitive complexity).	Healthcare professionals provide: ▪ a protocol for handling unsolicited findings of patients who are normally considered competent but who are impaired by their disease ▪ understandable, personalized and accessible information and education for patients and their relatives. ▪ personalized guidance and counseling; for example, supported by evidence-based decision aids. In addition, there is no time pressure during the decision phase.
Autonomy as a moral ideal	▪ *Self-determination* Almost all cancer patients expressed the wish to make individual decisions on the return of unsolicited findings. ▪ *Distinct self-identity* Although family members are frequently consulted for advice, it was emphasized that patients feel that the ultimate decisional authority is up to themselves. ▪ *Self-generation* Unsolicited findings were perceived as useful information to shape and adapt patients' future life plans. ▪ *Responsibility for self* Patients want to take responsibility for the course of their own life.	The starting point is a good relationship between patient and healthcare professional, based on trust, transparency, partnership, and attention to the patient's values and preferences. Healthcare professionals: ▪ foster patient autonomy as a valuable ideal. ▪ acknowledge traits of autonomy in their patients. ▪ shape favorable circumstances for cancer patients to be able to act autonomously. ▪ support patient empowerment. ▪ strive for shared decision-making encouraged by an equal relationship between healthcare professional and patient.
Autonomy as a personal right	▪ Patients wanted to be informed about unsolicited findings. ▪ Several patients expect that at least one of their family members doesn't want to be informed about genetic results.	Healthcare professionals: ▪ respect patients' and family's autonomy: for example, an informed consent procedure must provide the options "the right to know" and "the right not to know" for genetic test results (opt-in/opt-out).

[#] General observation and standard for practice (not a specific finding in our study).

Table 2. Dimensions of autonomy, our findings and practical implications

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Chapter 5

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

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Submitted

Abstract

Background

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

Methods

In a quantitative multi-center study, adult cancer patients (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).

Findings

In total 1072 patients were included, 701 participants completed the 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 - 5.37, reproductive significance: OR 1.97; 95% CI 1.05 - 3.67 and unknown significance: OR 2.00; 95% CI 1.25 - 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.

Interpretation

Our study showed that the vast majority of cancer patients 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 is useful to support patients in making informed decisions on UFs.

Introduction

Advances in genome sequencing have transformed cancer prevention, diagnostics, prognostics and treatment.[1,2,3,4,5] Although small gene panels are commonly used in current daily practice, whole genome or exome sequencing (WGS/WES) are gaining ground because 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 to small panels.[6,7,8]

In general, WGS/WES commonly also encompasses sequencing germ-line DNA as reference material, in order to aid the interpretation of genomic data. 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.[3,6,9,10,11] These findings may not only have medical, psychological, financial and social implications for patients, it may also 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 categorize 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 cancer patients 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 cancer patients 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 cancer patients 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, cancer patients were included in the OncoGenEthics study in the Netherlands. Participants were recruited from ten hospitals, affiliated with the Center of Personalized Cancer Treatment, a consortium of 49 hospitals in the Netherlands. During an outpatient visit, patients were offered an envelope by their oncologist containing an invitation to participate as well as background information 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 (PLCRC) and the Utrecht Cohort for Multiple Breast Cancer Intervention Studies and Long-term Evaluation (UMBRELLA) were invited by email.[15,16]
The research protocol was approved by the Research Ethics Committee of the University Medical Center Utrecht (The Netherlands), and 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 cancer patients.[13] The survey included sociodemographic questions, questions concerning patients experiences with genetics and tumor profiling and questions to assess health literacy.[17,18,19]
To ensure that participants had sufficient and the same background knowledge, two digital videos[13] 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 (respectively: actionable UFs, non-actionable UFs, UFs of reproductive significance, UFs of unknown significance, *Figure 1*). 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 Research and Treatment of Cancer-Quality of Life-C30 questionnaire EORTC QLQ-30.[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 after inclusion in the study if they had not yet completed the questionnaire.

Data analysis

The data were analyzed using Statistical Package for the Social Sciences, version 25 (SPSS Inc., Chicago, IL). For univariable analysis, Pearson's chi square and ANOVA were used to test whether participant characteristics were correlated with preferences regarding UFs. Furthermore, binary logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (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.

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

Results

Response

A total of 1072 cancer patients 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 one hour to complete. In *figure 2* we show the survey inclusion and participant numbers. 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%)) 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

Characteristic		N, %
Sex	*Male*	386 (45.7%)
	Female	455 (53.9%)
Cancer stage	*Curative*	311 (37.5%)
	Advanced-stage	519 (62.5%)
Mean age, y (SD)	*All participants*	59.9 y (11.1)
Age, y	*18-35 years*	30 (3.6%)
	36-50 years	113 (13.4%)
	51-65 years	414 (49.1%)
	66-79 years	273 (32.3%)
	≥ 80 years	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 (esophageal, stomach)	19 (2.3%)
	Sarcoma	16 (1.9%)
	Brain tumor	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 Inst.*	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%)
	Don't know	96 (11.5%)

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

Table 1. Patient characteristics

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* a selection of our univariable analysis is presented, the complete univariable analysis is presented in Supplemental 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 versus 258 (64.2%) women) and UFs of unknown significance (263 (87.7%) men versus 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 to women (non-actionable: OR 3.32; 95% CI 2.05 - 5.37); (reproductive significance: OR 1.97 (1.05 - 3.67)); (unknown significance: OR 2.00 (1.25 - 3.21)). Initially, curative participants were less likely to be willing to receive UFs (OR 0.56; 95% CI 0.32 - 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.
Higher educational level was associated with higher preference of receiving actionable UFs (OR 2.31; 95% CI 1.02 - 5.22) and lower preferences for receiving UFs of unknown significance (OR 0.59; 95% CI 0.41 - 0.85). Participants with living first 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 - 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 - 0.79) than participants without a religious conviction. For cancer subtypes, only participants with urogenital cancer had different preferences, amongst others less willingness to receive non-actionable UFs (OR 0.47; 95% CI 0.22 - 0.99) and UFs of unknown significance (OR 0.40; 95% CI 0.19 - 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 - 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 - 1.03), especially for UFs of unknown significance OR 1.01 95% CI 1.00 - 1.02).

Question		**Total group**	**Sex**		**Stage**	
			Male	***Female***	***Curative***	***Advanced stage***
In general, if (again) a genetic tumor	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 tumor 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 tumor 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 tumor 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 tumor 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 Chi-square p-value below 0.05

Table 2. Univariable analysis of the question whether or not to receive unsolicited findings

	UFs in general			**Category 1:** *actionable UFs*			**Category 2:** *non-actionable UFs*			**Category 3:** *UFs of reproductive significance*			**Category 4:** *UFs of unknown significance*		
	Exp(B)	95% C.I.for EXP(B)		Exp(B)	95% C.I.for EXP(B)		Exp(B)	95% C.I.for EXP(B)		Exp(B)	95% C.I.for EXP(B)		Exp(B)	95% C.I.for EXP(B)	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		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 (/y)	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		
1-2 years 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
> 2 years 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 HealthLiteracy	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 tertiar 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
Totalscore 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	**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 below 0.05

Table 3. Multivariate analysis of patient characteristics, basic demographics, disease- and social characteristics for patients wanting to receive UFs

Sharing information with family members

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

		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%)

Table 4. Patient preferences about sharing information with family members

Discussion

Our study shows that a vast majority (85.1%) of the cancer patients when asked to participate in genomics-guided treatment in the Netherlands prefer 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 participants would also opt for feedback of findings that presently are considered to be non-actionable. Nevertheless, there is also a substantial group (20.6%) of participants who does not wish to be informed about non-

actionable UFs. The same is true for variants of unknown significance (18.2%). 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 study population that cancer patients have a strong propensity towards learning about a wide range of genetic risk information, consistent with the enthusiasm for receiving genetic findings among the general public and with results from smaller studies among cancer patients.[23,24,25] 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.[6,26,27,28,29] The current results provide oncologists with tools for a personalized 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 pre-select a subset of UFs.[30] While 85% of participants initially responded positively to the question as to whether they desired disclosure of UFs in general, percentages in favor 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 an important 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 cancer patients 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.[13,31,23,24]

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.

To our knowledge, this study is the first large quantitative study to explicitly survey cancer patient preferences 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 emphasized 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 cancer patients.

Our study also has limitations. First, there is some imbalance in educational level (50.9 % participants have a college degree) and 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 toward patient 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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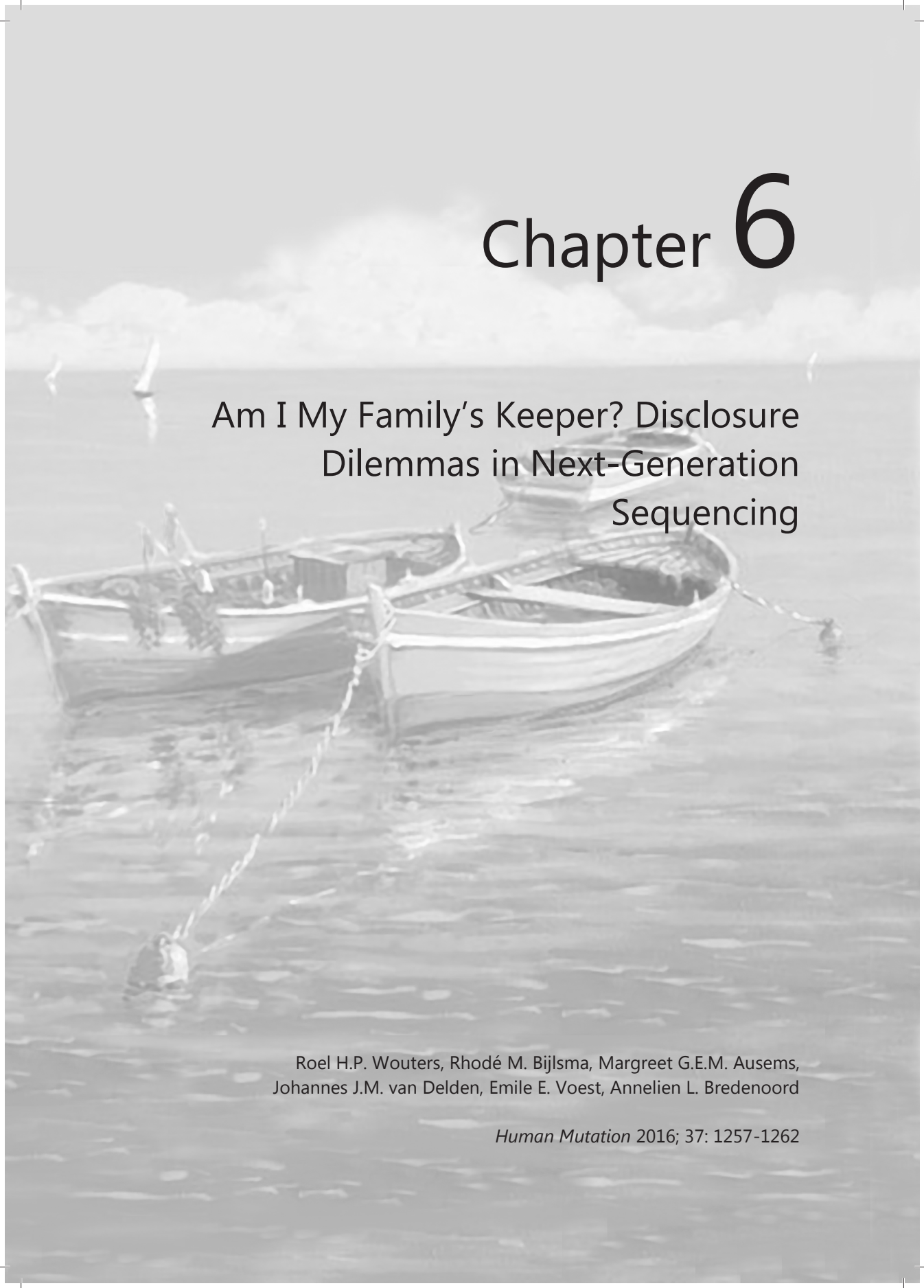

Chapter 6

Am I My Family's Keeper? Disclosure Dilemmas in Next-Generation Sequencing

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Introduction

Single gene testing is available for a few decades now. Since that time, healthcare professionals have been confronted with dilemmas that arise from the fact that genetic findings have implications not just for individual patients but also for their family members.[1,2] This debate has become increasingly urgent in the advent of next-generation sequencing (NGS) technologies such as whole-exome sequencing and whole-genome sequencing. NGS techniques are particularly promising in the context of personalized medicine.[3] In the near future, healthcare professionals will face more dilemmas regarding the disclosure of genetic test results to family members because more people will undergo genetic testing. An example of this development lies within the context of personalized cancer care, where germ line sequencing is an essential component in accurate assessment of actionable mutations in neoplasms. Although the chance of finding an unsolicited but actionable germ line mutation remains relatively low on an individual level,[4] the absolute number of unsolicited findings is expected to be considerable.[5,6] Consequently, the ethical dilemma of whether or not to communicate genetic results to family members directly will occur more frequently as NGS finds its way into clinical practice.

Current ethical literature focuses primarily on the scenario that a patient explicitly refuses to share potentially life-saving genetic information with relatives.[7-10] Indeed, a majority of genetic professionals have encountered this dilemma at least once in their careers.[11] Empirical research, however, suggests that the refusing patient scenario occurs in less than 1% of the consultations in the genetics clinic.[12] Generally, patients are willing to share relevant results with their family members. Moreover, the possibility to inform relatives about hereditary diseases is an important motivation for patients to undergo whole-exome sequencing. Until now, this has primarily taken place in a research setting rather than within a clinical diagnostics setting.[12-14] This article, therefore, concentrates on a much more common situation: a patient is not opposed to sharing genetic information but nevertheless fails to inform her relatives. Particularly urgent in this situation is information on hereditary diseases that can be cured or prevented. Although probands know that it is important to inform family members and are generally willing to do so, data suggest that this vital transfer of information often fails to occur.[15-17] Uptake of genetic testing tends to be quite low, approximately half of the relatives undergoes genetic testing after a potentially life-threatening mutation (e.g., HNPCC) has been found.[18] This suggests that index patients often do not adequately inform at-risk people in their families. Reasons for not sharing results include not feeling close to family members, not finding the right time and words, and anticipation of negative reactions.[19,20] Traditionally, there is a strong emphasis on the duties of the professional in this debate.[21,22]

But what is the role of the patient and her family? Family ethics is a domain in the field of bioethics that has not been given much attention, and only a few authors have dealt with the subject of responsibilities that arise within a family.[23] Whereas the current literature about

family ethics views the family as a community rooted in shared values rather than shared genes,[24] NGS draws the attention toward responsibilities that emerge within a genetic family. In this article, we examine the question of who is responsible for conveying actionable information to relatives of patients undergoing NGS.

The Professional's Responsibility

The underlying ethical justification for professionals to actively contact relatives that are at risk is a duty to warn.[10,25] A duty to warn is a specification of the duty to rescue. It dictates that in a situation where serious and imminent harm (e.g., a deadly disease) can be averted easily, that is, without high costs or risks for the actor, there is a moral duty to do so.[26] Applied to a genetic setting, people can be protected from significant harm when a mutation is likely to cause a life-threatening disease that can either be prevented or cured when the genetic aberration is discovered early.[8,27] A duty to warn can be conceived as a general moral obligation, not solely valid for healthcare professionals. Yet, this obligation is even stronger for healthcare professionals working with NGS, as they have special knowledge and skills about genetics. Moreover, this general knowledge is combined with detailed information about mutations that are found in the index patient. This specific knowledge and these skills, combined with the commitment to a specific code of professional ethics, can be summarized as a role-related responsibility.[28,29] Another aspect that highlights the importance of this role-related responsibility is public trust.[29] Applied to this specific context, a physician has the responsibility to warn people that they may have a preventable or curable genetic condition because the public expects this from a healthcare professional and the system she works in.

Thus, a duty to warn, especially when embedded in role-related responsibilities, is a compelling ground for healthcare workers to convey genetic risk information. Yet, this moral obligation is a prima facie moral duty, that is, it has to be executed in the absence of other compelling obligations. However, in this context, there are indeed strong conflicting duties that put moral limits on the duty to warn of a professional. Active disclosure may violate the patient's autonomy, because the confidentiality that exists within a doctor–patient relationship may be breached. On top of that, a policy that requires professionals or institutions to seek active contact with a large number of relatives can be excessively demanding because it puts tremendous constraints on time and resources.[30] Another conflicting moral duty is the right not to know. This is a major concern that dictates caution, especially regarding the communication of genetic results to relatives, since they are not able to express a wish (not) to receive those results. It seems impossible to inform them that there is a reason to get tested and at the same time to give them the opportunity to live a life without worries about hereditary diseases. It is important to note, however, that the right not to know needs to be activated in some way. One cannot invoke this right without any previous knowledge that something could be wrong.[31,32]

In conclusion, there is a rationale for a professional moral responsibility to inform at-risk relatives, yet moral and material costs associated with such a practice have to be taken into consideration as well. On a policy level, this accounts for a difficult situation: the duty to warn can be a legitimate reason for a physician to contact relatives in individual cases but to translate this into general policy is too complex and far-reaching. Too complex because balancing a duty to warn against conflicting duties is a process that is different for every situation and individual. Whether disclosure is appropriate depends on situation-specific factors, such as the seriousness of the condition, the imminence of its threat, the effort that is needed to reach family members, and so on. This contingency hinders the formulation of a sound universal policy, which is also manifested in the notable legal differences between countries.[33] The French jurisdiction, for example, imposes a legal duty on professionals to urge patients to inform relatives. The professional is not permitted, however, to circumvent the patient and contact family members directly.[34] By contrast, the Australian legal system sanctions direct communication between doctors and relatives in case of a serious threat even without the patient's consent.[35] This recent amendment to Australian privacy legislation has sparked fierce ethical debate, most importantly because it violates medical confidentiality in a way that is irreconcilable with contemporary professional standards.[36] To claim that it is a hospital's or physician's responsibility to contact every single relative is also too far-reaching, especially when broad introduction of NGS into clinical care will increase the number of unsolicited findings that professionals encounter. A professional cannot be expected to devote her entire schedule to searching for a set of relatives on Facebook or Twitter. If a structural solution cannot be provided by the professional, we have to consider the role of the patient. For now, we conclude that a healthcare professional working in the field of genetics has a generic and role-related responsibility, but is confined by conflicting duties and considerations of feasibility.

The Patient's Responsibility

The fact that a person is embedded in a family and therefore generally knows the specific composition and background of that family is what makes the patient unique in light of sharing actionable genetic information. So when discussing the patient's responsibility, what we are actually referring to is the patient's responsibility as member of her family. There are roughly two approaches to assessing the index patient's duties toward her relatives: the responsibility from interdependency and the responsibility from special relationship.

Responsibility from Interdependency

The duty to warn, as described above, applies not only to a professional but also to people in general. The underlying rationale of the duty to warn is equally valid for laymen. The index patient may lack weighty information or has limited understanding about the nature and seriousness of a certain mutation, but does have insights into the particular situation of her

own family. To give a very basic example: the patient knows who her family members are, information that most physicians can only acquire with help of the index patient. Even the general practitioner's (now electronic) card-box usually covers only part of the family that is susceptible to a genetic disease. Furthermore, a patient may generally be able to judge whether a certain relative is willing to receive such a warning and is psychologically stable enough to do so. Responsibility from interdependency is based on reliance rather than on a particular relationship. The following example is often used to illustrate the duty to warn (derived from a duty to rescue): a child falls into a ditch and needs help from a bystander to prevent it from drowning. Like the bystander along the side of the ditch, a brother who has vital genetic information has a moral duty to rescue his sister by informing her about the mutation. He has a moral obligation to do so because he is aware of the threat and able to save her, not because they grew up together. In this line of reasoning, the only necessary condition for a moral duty in such situations is the information about a genetic disease and the knowledge that a certain relative may carry the same mutation. Surely, there may be additional arguments that take into account that brothers and sisters (or parents and children) do have a special relationship. These arguments will be elaborated upon in the next paragraph.

Responsibility for Special Relationship

Instead of concentrating on general and universal moral principles, care ethics emphasizes the question of how to respond to the needs of particular "others" in life such as relatives .[37,38] Weaver applied the ethics of care to disclosure of genetic information to relatives. She argues that an ethics of care tells the physician to foster her relationship with the patient and respect the patient's considerations on what is good for her own relatives, instead of putting that relationship at risk by breaching confidentiality and consent. While Weaver uses this perspective to emphasize the preservation of a doctor–patient relationship, care ethics can also be interpreted as a plea for responsiveness of patients toward needs of her family. The focus of care ethics on special relationships is indeed a useful perspective because, to many people, family is the kind of relationship that care ethics describes as central to the moral obligations of individuals.[39] In a slightly different context, namely, filial obligations to care for elderly parents, Stuifbergen and van Delden have made a similar point that there is a duty to care for people who depend strongly on the acts of a particular person. From this perspective, special relationships are meaningful not only emotionally but also in a moral sense: it creates duties vis-à-vis persons that are close to us.[40]

An analogous line of reasoning can be found in the domain of Confucian ethics. Arguments drawn from this realm are similar to care ethics in that they focus on obligations arising from our deep and meaningful entanglements, but are rooted in a distinctive tradition. The special position of the family is a central feature in Confucian ethics.[41] Recently, several scholars have made propositions to implement these family-centered approaches into medical practice.[42-44] Instead of taking the individual (e.g., the index patient) as a starting point,

Confucian ethics puts the family first: "Chinese bioethics is not primarily focused on the individual; but rather concern for the individual is shaped within the structure and moral authority of the family".[43] Lee argues that within such a structure, sacrifices of the individual are sometimes required and helping relatives is a moral duty that arises from the intimate ties within a family.[44] Although the particular issue of disclosure of genetic information has not been addressed (at least not in English literature) by scholars following the Confucian ethical tradition, the obligation of a patient to share these results fits well within the framework of sacrifices that an individual ought to make as a member of a certain family.

What is the value of these arguments that invoke the notion of special relationship? Both care ethics and Confucian ethics draw attention to the argument that one should not conceive the patient as an individual who makes decisions entirely on her own, that is, independent of other people. However, these special obligations seem to emerge from a conception of the family that views the family as a value-community instead of a genetic community. In the context of NGS, it is the genetic relationship that is crucial. A genetic relationship cannot be expressed in terms of emotional closeness, shared experiences, or mutual expectations. The value aspect of a family is meaningful to many and for those people that special relationship will be a persuasive ground to share genetic results. It is, however, precarious to base a patient's moral responsibility entirely on this special relationship. A duty to warn would apply even to genetic relatives that do not live in the intimacy of a traditional family. For example, the fact that a cousin is living abroad for her entire life is not a reason not to inform her about a BRCA gene that is found in the index patient. A notion of the family as an environment where individuals flourish presupposes a model of the family where children are raised and elderly (grand)parents are cared for. Cousins and nieces grow up outside such an environment, but their interests in receiving genetic results are obvious here. Situations of non-paternity are also part of this category. Conversely, an adopted son is a full member of the family as a value-community, but his genetic background is completely irrelevant for the issue that is discussed here. A special relationship may be (and often will be) a compelling additional reason for patients to disclose. However, it is not a necessary condition, nor is it a sufficient ground for moral obligations in this context. Not necessary because a duty from interdependency is important also in the absence of close family ties. Not sufficient because that relational bond is relevant only in cases where there is a genetic connection. To put it differently: with regards to the issue at stake, the patient's responsibility as member of a family is essentially DNA based rather than intimacy based. The observation that lack of proximity is a common constraint on adequate disclosure within a family illustrates this point.[20] Arguments derived from a special relationship cannot solve this problem, because they are specifically grounded in the factor that may be lacking: closeness.

Balancing Professional and Patient Responsibilities

From the analysis above, we conclude that both the healthcare professional and the patient have a duty to warn relatives that are at risk for hereditary diseases that can be cured or prevented. However, the physician has strong conflicting duties, such as the duty to respect medical confidentiality, that restrict the fulfilment of this obligation. Moreover, as Weaver suggested, the professional is usually not aware of the specific circumstances of the relatives in question, a knowledge gap that might result in serious psychological harm that could otherwise have been avoided.[39] Examples of precarious situations are serious mental or physical health conditions and non-paternity. Altogether, a physician can only fulfil her duty to warn with assistance of the index patient. The patient serves as an essential actor in fulfilling both her own and her physician's duty to warn. Yet currently patients are often not sufficiently empowered in terms of counseling skills and medical knowledge to provide the right information adequately and prudently.[17] That is why we are in need of a strategy that acknowledges both the patient's and the professional's duties, but also the limits to these obligations. In pursuing such a strategy, we invoke the idea that people's choices can be adequately influenced without interfering with their personal liberty and responsibility to choose: nudging.

A Libertarian Benevolence Strategy: A Nudge Toward Disclosure

A strategy to influence people's behavior in a non-coercive way encompasses libertarian paternalism.[45] This approach has found its way into the field of public health, for example, for promoting a healthy diet and smoking cessation.[46,47,] Recently, we explored the application of nudging to disclosure of unsolicited findings to patients.[25,48] The justification of libertarian paternalism starts with the observation that people do not always know what their preferences are, do not always choose rationally, and sometimes lack self-control. Furthermore, the choices of an individual are influenced by the framework within which these choices are provided to them. Starting points and default options guide our behavior all the time. These framing effects are, at least to some extent, inevitable. Libertarian paternalism proposes that policy makers can steer people in a certain direction by changing default settings without blocking other options. This is paternalistic in the sense that people are actively encouraged to choose for the option policy makers find prudent, but at the same time libertarian because in the end no options are being closed off. This strategy can also be used to encourage people to make decisions that are good for other persons, a variant that is called libertarian benevolence.[45,49] Libertarian benevolence also uses nudges to steer people's behavior in a direction that promotes the wellbeing of others. A nudge usually entails the setting of a default decision (that can be altered) or a framing of language.[50,51] For the purpose of disclosure of genetic information, we propose an intervention that fits within the framework of libertarian paternalism and incorporates

insights from our analysis on patient and professional responsibilities: the moral accountability nudge.

Our earlier proposals that apply nudging to the field of genetics entail default nudges, for example, an opt-out rather than an opt-in for passive disclosure.[30] There are good reasons, however, that the informed consent procedure contains not only a default nudge but also a moral accountability nudge. A patient who underwent NGS and received results about hereditary conditions is probably the only person who can share this knowledge with family members. This is because a physician does not have the tools to check whether the patient has shared the genetic information, and should not desire to have such a possibility either. Patients should be made aware of this responsibility. In this case, it is not enough to merely inform persons. They have to be urged to make a particular decision: to convey the information to genetically related family members. Disseminating the information is an important moral duty of the patient, and the nudge we propose articulates this. Obviously, all support in terms of information and counseling should be offered. Such a nudge is somewhat paternalistic in nature, as it contains a form of persuasion to influence people's behavior. This form of directive counseling fits well in what Emanuel and Emanuel have called the deliberative model of the physician–patient relationship, where persuasion rather than coercion is used to influence a patient's behavior.[52] Although persuasion in an informed consent procedure is usually considered to be inappropriate,[53] we argue that it is justified in this particular situation because the health of relatives that are at risk cannot be guaranteed in a different way. As mentioned above, the patient has a duty to warn as relatives depend entirely on the assistance of this particular patient. The professional has a duty to encourage her patient to warn family members, a moral obligation that cannot simply be met by informing and offering additional counseling. A moral accountability nudge emphasizes the active role that the patient is expected to play. As additional support, patients can be offered an option within which first- and second-degree relatives are contacted by the institution if a person is unsure whether she is able to inform other persons. Yet, it should be clear that this is a means to satisfy a patient's responsibility, not a transfer of responsibilities to the professional. This option also requests an active contribution of the index patient, who should deliver information that can be used to contact relatives. The moral accountability nudge's emphasis on the role of the patient expresses the view that the patient is not merely a client but also a moral actor. The nudge we propose aims toward an increased awareness among (index) patients that they have a role in preventing harm to their relatives, and the moral demands that accompany such a role.

A common critique to libertarian paternalism is that it would be incompatible with the common prerequisite of autonomous decision-making. According to this view, a nudge interferes with the patient's ability to make choices aligned with their own goals and values in life.[54] Conceived this way, libertarian paternalism cannot be an ethically sound addition to the practice of genetic counseling, because it allegedly imposes the physician's values upon the patient. We do not think that this critique is convincing with regard to the particular

application of nudging that we propose. Empirical studies have shown that certain barriers hinder adequate communication of relevant genetic results between relatives. These barriers include fear of upsetting people, not being in contact with relatives or not being emotionally close to certain at-risk family members.[55-57] Those obstacles are to be taken seriously, but for many people they are not based on deeper values or beliefs. Instead, a vast majority of the patients seen in the genetic clinic find it important to share test results. Yet, due to circumstances in life and restraints embedded in human psychology, people have difficulties putting this into action. Libertarian paternalism, as it was originally developed, starts with the observation that people often do not make choices aligned with their actual preferences. For example, they tend to be excellent in procrastinating difficult but important things (a situation very familiar to many of us), and nudges might help them to overcome their inactivity.[50] In the application we propose, we aim to nudge people's behavior not only toward what we think is morally right but what probably reflects their own moral beliefs as well—and if not, they are always free to opt out from the nudge (which makes it libertarian paternalism). A moral accountability nudge appeals to values people already cherish, and convinces them to translate those beliefs into action by making them realize their unique role as a moral agent. We stress that this nudge is a means of persuasion, and manipulation should obviously be avoided. A nudge that supports people to make decisions in accordance with their deeper values does not infringe upon an individual's autonomy.[58] This article discusses the moral accountability of professionals and patients, but we are aware that our strategy may influence the legal debate as well. However, imposing penal liability on patients does limit their autonomy in a way that cannot be warranted from the perspective of libertarian paternalism. Threatening patients with prosecution by a third party (the government) may distract the attention from decision-making as an independent moral actor rather than emphasizing it. Consequently, we think moral accountability should be distinguished from legal liability. A moral accountability nudge, combined with counseling services such as online tools, information letters and additional consultation sessions, raises consciousness in patients that they have a unique moral responsibility and this realization helps them to overcome those barriers.

Conclusion

Disclosure of genetic information to relatives has been discussed comprehensively in literature. The focus, however, has been on the question whether patient confidentiality can be breached in order to warn relatives directly that they are at risk for hereditary diseases. Our article concentrates on a slightly different but probably more prevalent situation: a patient is not opposed to disclosure, but nevertheless important information about preventable or treatable diseases is not passed on. This is a pressing issue as NGS is now being implemented in daily clinical practice and is likely to result in an increase of actionable unsolicited findings. Traditionally, there is a strong emphasis on the duties of the professional in this debate. The professional has a duty to warn but is also restrained by the

confidentiality of the doctor–patient relationship. Moreover, to burden the professional with the responsibility of actively informing all the patient's relatives that might be at risk is an overly demanding requirement. A patient who received testing also has a moral obligation that is grounded in the same rationale: a duty to warn. This duty to warn is based on a duty to rescue that arises in situations where people depend strongly on one other's help: if one is able to prevent serious harm in a relatively easy way, there is a moral obligation to do so. Additional arguments for a patient's responsibility with regard to this issue are based on the special relationship that individuals have within a family. A moral accountability nudge, grounded in the framework of libertarian paternalism, provides an alternative strategy that encompasses both the professional's and the patient's responsibility. We provided the moral rationale for such a nudge. As the patient is an essential link between the professional and the relative, the professional needs the compliance of the patient to fulfil her own duty to warn. By making the patient aware of this special responsibility and by stressing its importance, the patient can be nudged in the right direction. In a time where the use of genetic testing is rapidly expanding, we need this kind of policy that is both feasible and responsive to the responsibilities of all the actors involved. After all, in genetics we are our families' keepers.

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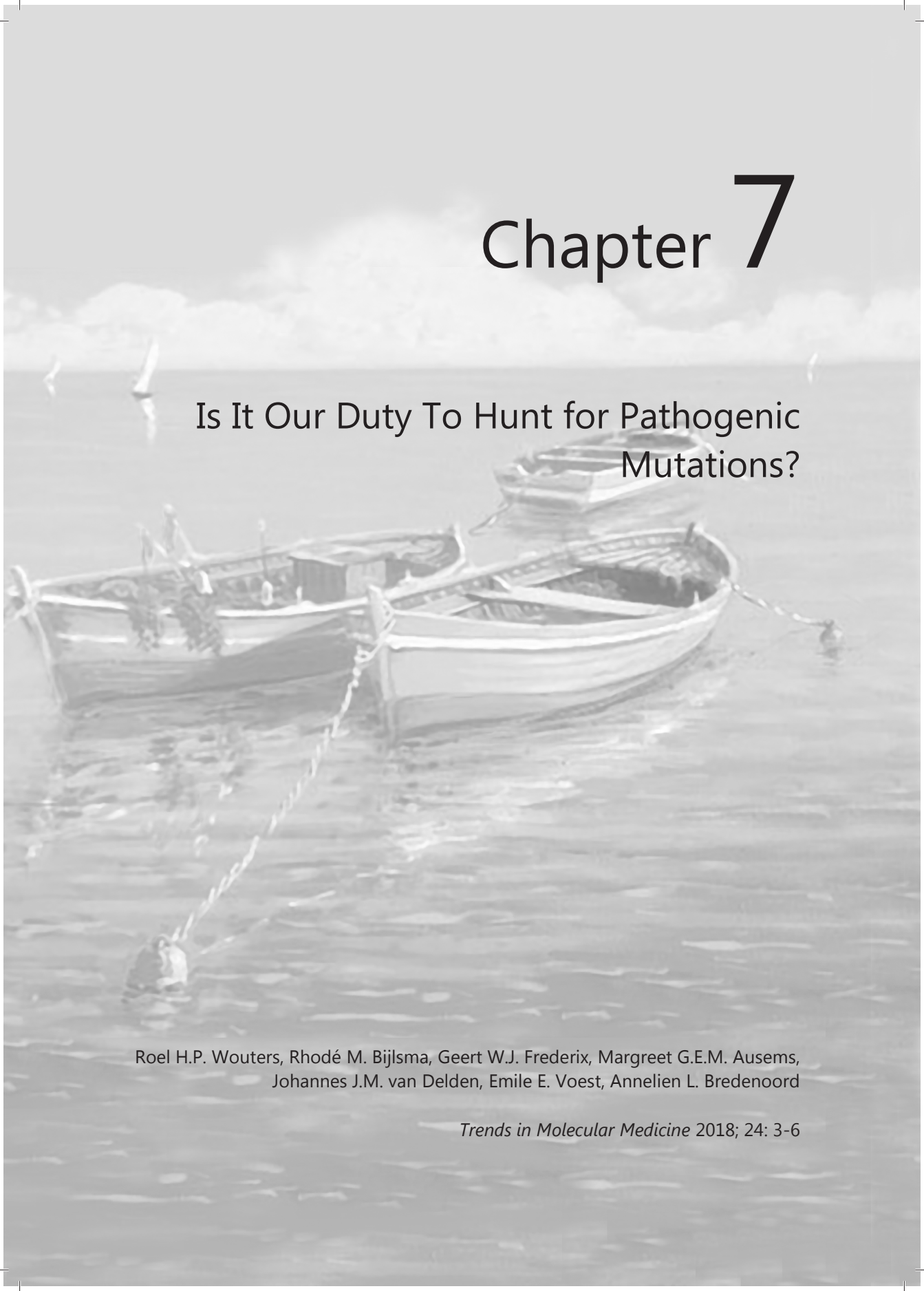

Chapter 7

Is It Our Duty To Hunt for Pathogenic Mutations?

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Abstract

Should professionals systematically screen whole-genome sequencing (WGS) data to check for life-threatening mutations? Alternatively, should genome analysis focus on the primary reason for testing – that is, aiming to achieve precision medicine? We present an ethical review of the arguments and compare the act of searching for mutations with disclosing mutations that are discovered incidentally.

Whole-Genome Sequencing: Systematically Searching For Mutations Versus Incidental Findings

Medical professionals may be confronted with a large flow of data generated by an increased use of Whole-Genome Sequencing (WGS) and whole-exome sequencing in basic research and clinical practice. WGS yields a substantial collection of data, containing information that is both related and unrelated to the initial clinical or research question. This batch of raw sequencing data may be meaningless unless converted into interpretable results, raising the ethical question of which data should be analyzed and communicated to the patient.[1]

Many professionals support feedback of medically relevant findings that are encountered incidentally – at least, those that are considered actionable (for instance genetic mutations that predispose a patient to conditions that might be treatable, such as BRCA1/2 mutations).[1-3] Highly contested, however, is the question of whether professionals also have a duty to actively search genomic data for disease-relevant mutations.[1,3,4] This policy has been generally referred to as 'opportunistic' or 'routine' screening, although opponents have called it a 'duty to hunt.[1,3-5] The American College of Medical Genetics and Genomics (ACMG) advocates routine screening, a recommendation that remains controversial even though the ACMG has responded to criticism by allowing patients to opt-out from receiving feedback.[5,6] The European Society of Human Genetics (ESHG), among others, has petitioned for keeping genetic testing as targeted as possible.[7] Meanwhile, clinical and basic research practice is trapped between these trenches. Therefore, in this article we discuss the ethical arguments for and against routine screening (Table 1).

Beneficence Versus Non - Maleficence: Saving Lives or Imposing Risks?

A potential benefit for patients appears to be the leading argument in the ACMG statement, which emphasizes the importance of discovering life-threatening genetic mutations for the health of patients and their families.[5] In addition, surveys among patients show that a vast majority of the respondents want to learn about actionable findings, a strategy that is also supported by many professionals.[2]

Tracking down these mutations is also believed to advance scientific knowledge by generating genomic findings that can be used for further research.[8]

The projected benefit of routine screening is, however, criticized because genomic information may also be harmful to the patient, especially because many mutations on the ACMG list are poorly studied in the general population. Specifically, risk estimates are often calculated based on studies of families or patients at risk of carrying a disease-causing mutation, which in turn might potentially result in overestimating the risks. Detection and communication of these mutations may lead to unnecessary surgeries and complications,

unjustifiably reassuring patients that not carrying a mutation might signify not developing a disease, or possibly generating undue anxiety and financial preoccupations (e.g., insurance problems).[4]

Theme	Arguments for	Arguments against
Beneficence	Routine screening: - potentially save lives - yields information desired by patients - is supported by professionals - contributes to scientific progress	Information generated by routine screening may be unwarranted due to: - complications of (unnecessary) preventive/prophylactic interventions - false reassurance - psychological harm - financial consequences - lack of evidence for clinical utility
Costs	- Long-term cost reduction due to improved scientific evidence - May avoid expensive treatments because of early detection and prevention	- Additional costs due to interpretation, post-test counseling, and necessary follow-up
Equal access	- Routine screening is part of a consistent sequencing procedure that treats all sequenced genomes from patients equally - Patients can also gain access to their genomic information through raw sequencing data	- Routine screening may be unfair because it grants genetic risk information only to a limited group of patients

Table 1. Debating Routine Screening of Genomic Testing Data

These risks are regularly mentioned in these debates, although empirical support for these claims is often lacking. For example, patients are more psychologically resilient than many professionals expect: long-term anxiety or depression upon receiving information on disease-causing mutations has rarely been observed.[9] Similarly, insurability problems might be frequently feared, but are rarely reported.[10] However, it is impossible to predict whether individuals will face genetic discrimination under future legislations.

These potential adverse circumstances urge caution in the implementation of routine screening. Nonetheless, unsolicited findings that have been serendipitously 'stumbled upon' may cause the same types of adversity. Hence, if potential harm from receiving information on mutations would be a decisive argument in the debate on routine screening, then unsolicited findings should never be disclosed. However, this runs contrary to the consensus regarding unsolicited findings, which now leans towards offering disclosure – at least for actionable mutations.[1-3] If feedback on actionable mutations is considered beneficial, then

actively searching for these precise mutations may be equally beneficial. Therefore, risk arguments alone might not preclude being able to screen for a list of mutations. Instead, risk–benefit ratios of specific mutations – together with other criteria such as patient viewpoints – might be used for multidisciplinary boards to decide whether such specific mutations should be included on a list for routine screening.

Costs of Analysis, Interpretation, and Follow-Up

Some authors have argued against routine screening because it is either too costly or too time-consuming.[3,11] Routine screening encompasses similar, but also additional, costs compared to the policy of disclosing unsolicited findings; these costs may further increase the burden on healthcare budgets (Table 2).[12,13] In part, these costs might be mitigated by accounting for the possibility of preventing disease and securing timely treatment options.[12] The extent to which these costs might burden healthcare in the future remains largely unknown because robust data on the economic costs of routine screening and disclosure of unsolicited findings are currently very limited. The establishment of economic models relies on reports that reveal the clinical validity and utility of screening genomic datasets; at present, these reports are often inconclusive.[13] The resulting economic uncertainties pose a dilemma for professionals who might have to decide, from a financial perspective, whether these uncertainties require routine screening to be suspended entirely until proven cost-effective, or whether routine screening can be carried out during the time needed to establish such economic evidence.[8]

There may be at least two arguments to provisionally accept routine screening. First, the implementation of routine screening may produce data that yield more robust evidence on the disease association of particular genomic characteristics in a general population.[8] Second, in the absence of definitive economic assessments, patients and professionals should be granted some discretion to act upon what they believe is right; we posit that, if both parties wish to elicit potentially life-saving information, they should be allowed to do so. Given that contemporary genetics is riddled with (economic) uncertainties, many of which are likely to last, demanding comprehensive economic evaluations as a prerequisite for introducing routine screening into the clinic may be unrealistic.

Equalizing Access to Genetic Information

Another objection to routine screening is that it may be unfair because it can grant access to germline information (e.g., on mutations that cause cardiovascular conditions) to patients for whom WGS is being performed based on an unrelated indication (e.g., personalized cancer treatment); by contrast, this access would not be ordinarily granted to individuals whose genome is not being sequenced, but who would nevertheless benefit from receiving information on their genetic risks.[11]

However, this line of reasoning fails to acknowledge that professionals bear responsibilities regarding the care of their (own) patients. In the clinical setting, physicians serve as advocates for the health of their patients. As a result, professionals might be rightly hesitant to deny their patients access to genetic results from their previously sequenced material because it could be construed as an unfair process vis-à-vis individuals who are not their patients and/or whose genome has not been sequenced, especially when considering that there may be a potentially unique opportunity to obtain life-saving information.[3] Presumably, patients might also expect routine screening to occur, failing to understand that although additional (unsolicited) genetic findings might be discovered, this is not always the case.[14]

Type of costs associated with routine screening	**Costs higher compared to disclosure policy?**	**Explanation**
Pre-test counseling	No	Every WGS procedure requires informed consent to be obtained for disclosure of unsolicited findings before sequencing
Sequencing and bioinformatic processing	No	Routine screening is the routine analysis of data already produced in the sequencing process
Medical interpretation	Yes	Routine screening requires additional time and effort to interpret findings by reporting on medical relevance
Post-test counseling	Yes	As more mutations are discovered, more (human) resources may be needed to explain the data to patients
Follow-up	Yes	More mutations requiring clinical follow-up may be discovered, and may necessitate: Additional tests to confirm genetic test results Preventive screening to monitor at-risk patients Prophylactic interventions to minimize risk

Table 2. Overview of WGS Routine Screening Costs

This is hardly surprising: solid pre-test genetic counseling already requires professionals to spend considerable time explaining all the pros and cons of receiving particular (categories of) unsolicited information. There may also be a degree of 'sloppiness' or 'haphazardness' in solely disclosing medically relevant findings that are discovered incidentally. From this perspective, incorporating routine screening into the workflow might not cater additional services to a specific group of patients. Instead, routine screening might be viewed as an integral part of regular sequencing procedures aimed at fulfilling the expectations of the patients. This approach would entail treating patients equally, ensuring that all patients whose samples are sequenced receive appropriate feedback on actionable findings. By contrast, a policy which dictates that unsolicited findings should be disclosed, but not actively searched for, might introduce the possibility that detecting pathogenic mutations

may occur by chance. However, if communicating these results to patients is truly important, as many have argued, we should not treat unsolicited findings as being left to chance. Finally, patients can always demand access to their raw data and request that their genomic information be reanalyzed (either individually using open-access software or by contracting a third party).[15] Therefore, even if routine screening is rejected, it may not rule out inequalities between patients whose genomes have been previously sequenced relative to those who have not undergone WGS before. Although potential disparities in access to genomic information and services between patient groups is a relevant concern for the field of genetics in general, we conclude that it would be unjustified to dismiss routine screening for reasons of potential unfairness.

Concluding Remarks: Next Steps

The enduring disagreement among professionals highlights the notion that genomic data (including its inherent uncertainties) might be evaluated differently by individuals with heterogeneous values and beliefs. Therefore, we propose that the way forward to resolving the debate on routine screening may be to acknowledge that patients, like professionals, have different, albeit legitimate, views from a medical and ethical standpoint. The ESHG has rightfully criticized the ACMG proposal by stating that routine screening is not a technological imperative.7 However, as discussed, opting for a strictly targeted approach does not seem to be imperative either. Unless future research shows that routine screening is detrimental for patient health, or for affordable and accessible care, routine screening might be allowed to constitute a part of an ethically responsible sequencing workflow. We propose that routine screening in the clinic should, at least initially, be limited to life-saving findings so as to avoid overburdening the healthcare system by unexpected financial costs that cannot always be anticipated at this point. This scheme might be expanded to other categories of genomic data, such as medically relevant but not immediately life-saving findings (e.g., genetic risk estimates on Alzheimer's disease), based on the information gained during this first phase. In the long run, the right question for professionals may not be whether providing access to genomic information is acceptable, but how to provide adequate support for patients who gain or wish to gain access to these data, while sustaining the functions of the healthcare system. Accordingly, policies should also take into account specific characteristics of the healthcare system, including budget restraints, as well as compliance and privacy issues. In this balancing process the agreement on disclosing unsolicited findings might serve as a model for establishing a routine screening policy that relies on medical experts as well as on patient choices for decision making. The aim of precision medicine is to gradually tailor therapeutic treatments in a personalized manner. Thus, a next step may also be to personalize our approach to information-sensitive genomic data.

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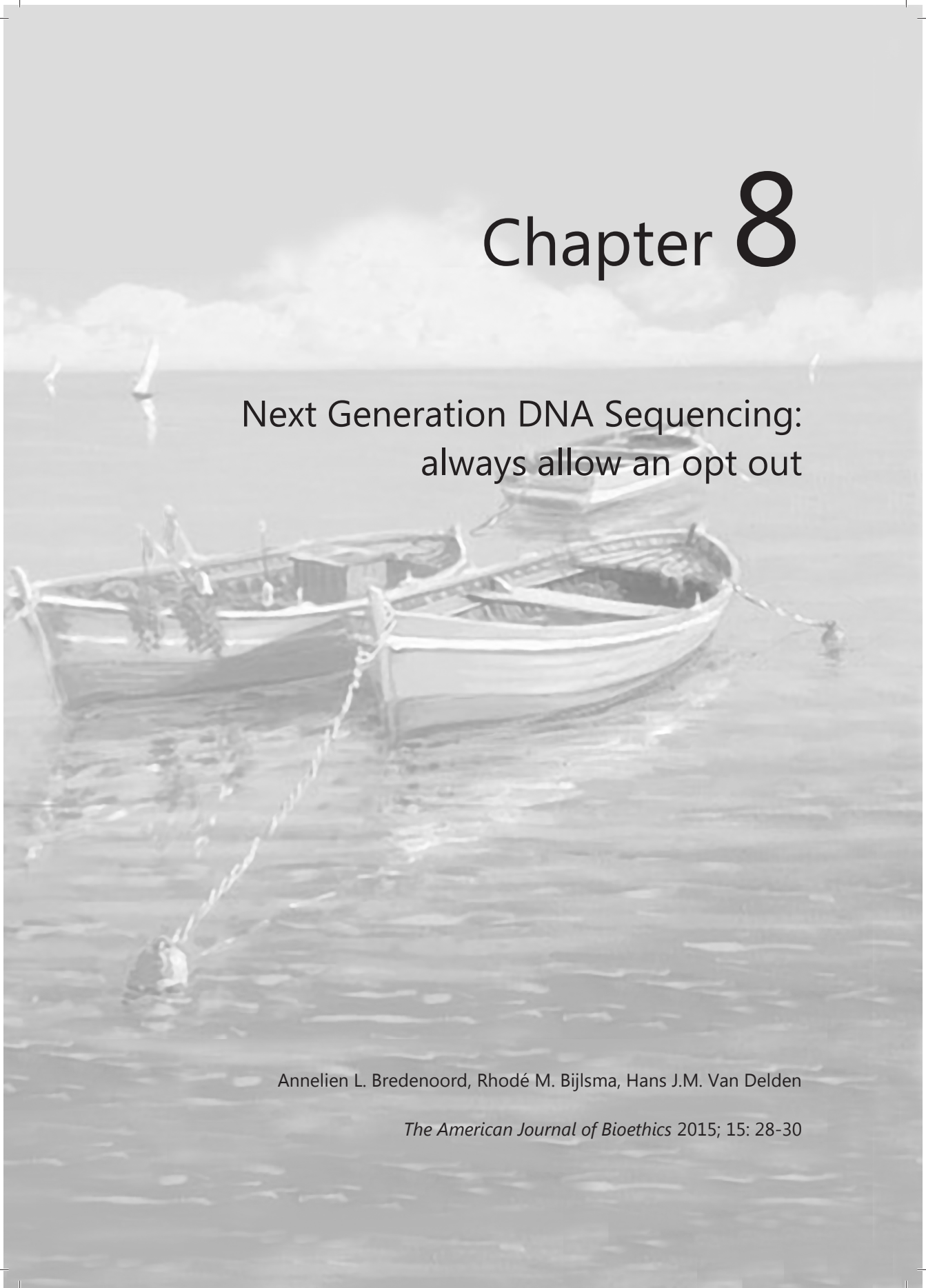

Chapter 8

Next Generation DNA Sequencing: always allow an opt out

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Return of results: an ongoing debate

With the rapid development of next-generation sequencing (NGS) technologies, among which whole exome and genome sequencing, it is now possible and affordable to sequence genomes in a short period of time. NGS has the promise to personalize treatment for patients in many fields, including cancer care. In oncology it is now common for studies using NGS to compare germ-line DNA with tumor DNA to filter relevant somatic mutations.[1] This facilitates a better selection of patients for a specific treatment. It may however not only generate information relevant for the disease in question, but also a wide variety of other findings including validated and non-validated, highly and poorly predictive information that may relate to all kinds of different disorders.[2] Whether and if so what kind of genetic risk information should be returned to patients undergoing NGS has been a matter of considerable debate. An emerging consensus now exists that (specific sets of) genetic information should be disclosed to patients, but the debate continues regarding the kind of genetic information that should be eligible for disclosure, how disclosure should take shape and whether genetic information *must* be disclosed, even when a patient has indicated not to want any feedback. Lázaro-Muñoz and colleagues discuss whether the application of NGS should allow individuals to opt out from receiving (specific sets of) genetic information. Earlier, recommendations of the American College of Medical Genetics and Genomics (ACMG) evoked debate right on this point:[3] should patients be free to decide themselves whether they want to learn genetic results? The ACMG suggested a minimum list of 56 genes that should be routinely and mandatory reported to patients undergoing NGS. After much criticism the ACMG later decided to adapt her recommendations.[4] Here we argue why any genetic disclosure policy should be a default based opt-out system.

Qualified disclosure policy

Earlier we have proposed a qualified disclosure policy based on tiered consent.[1,5] This policy contains a standard default package that is routinely offered to patients, possibly supplemented with additional packages such as reproductive information and late onset disorders. This policy is 'tiered' for it offers patients choices between different packages or categories. The default package minimally contains lifesaving data and data of immediate clinical utility that entail a significant health problem. The results should be analytically valid, actionable and accurate.[5] The default package is routinely offered, but patients are always allowed to opt-out for receiving genetic information arising from the default package. Most if not all patients will have difficulties with making a reasonable selection out of the wide array of possible genetic findings. The quantity, significance, and ambiguity of the genetic data generated by NGS will make any reasonable choice beforehand highly complex.[5] Therefore, our qualified disclosure policy balances the difficulties people may have with unrestricted result selection on the one hand with autonomy on the other hand. After all, insights from behavioral economy and decision-making theory have shown the limits of

ever expanding choice, resulting in information overload rather than autonomous decision-making.[6,7] Offering patients the possibility to decide about any potential variant might result in what has been called the paradox of choice: 'having no choice makes us unhappy, having some choice makes us happy, having too much choice makes us downright unhappy'.[6] We have therefore proposed to work with a default based opt-out system, where specific sets of genetic information are pre-structured in packages.

Liberal paternalism

Our default based opt-out system is grounded in what Thaler and Sunstein[8] coined "libertarian paternalism". We however prefer to use the term *liberal* paternalism as "libertarian" is an uncommon term in many European political systems. In our sense, "liberal" better covers the initial meaning as described by Thaler and Sunstein, embracing individual liberties and freedom of choice. Our qualified disclosure policy is liberal in the sense that patients are still free to choose not to receive genetic information, even if this may appear unreasonable from a medical perspective. Freedom wouldn't be freedom if we are only free to do what others think is reasonable. At the same time our policy could be called soft paternalistic because of the existence of the default package. The justification for this lies in our assumption that it is generally beneficial for people to receive those results and that they therefore should be offered in the default package. As mentioned above, making a selection out of the wide array of genetic information is highly complex. In these circumstances, a form of paternalism could be justified as long as it remains a variant of soft paternalism, or, in other words, as long as people are still free to opt out.

If the default package contains such import genetic information, why then allow an opt out? Although we assume that the majority of patients are willing to receive not only the default package but also additional packages, which is confirmed in studies as well,[9] patients do not have an obligation to learn genetic information. In our clinical practice in the Oncology department of the UMC Utrecht, it is our experience that some patients still have various legitimate reasons for not wanting to receive this information, including information about life-threatening diseases and diseases that strongly affect quality of life. Some palliative patients only undergo NGS for research reasons, and they sometimes indicate that they do not want to be confronted with genetic information. Others do not want to receive information that is only based on risk predictions with no certainty of occurrence in the near future. Such knowledge, in their view, is such a mental burden that they rather do not want to know. Other patients prefer only to receive limited selection of results. For example, only information that is actionable or relevant to their current underlying disease, but no information on diseases that are not treatable yet, and on genetic variants of unknown significance. Research in other contexts has shown that up to 75% of people who know they may be at risk for serious genetic predisposition for breast cancer refuse genetic testing, for reasons of avoiding psychological harm, fear of discrimination and reproductive reasons.[10]

We are aware of the difficulties this may pose for health care professionals when they are confronted with genetic information that cannot be returned to patients. Packages of genetic information that patients do not want to receive should therefore not be analyzed at all, if possible. This can be managed in a similar way as is suggested in pediatric NGS, where children are not offered late onset information in view of their right to an open future.[11] The use of filters can be useful here, but other avenues need to be explored as well.
In sum, the clinical introduction of NGS has the promise to personalize treatment for patients in many fields, but patients do not have an obligation to learn genetic information. Any disclosure policy that works with defaults may assist people in making a selection out of the wide array of complex genetic information but this should always be paired with an opt out.

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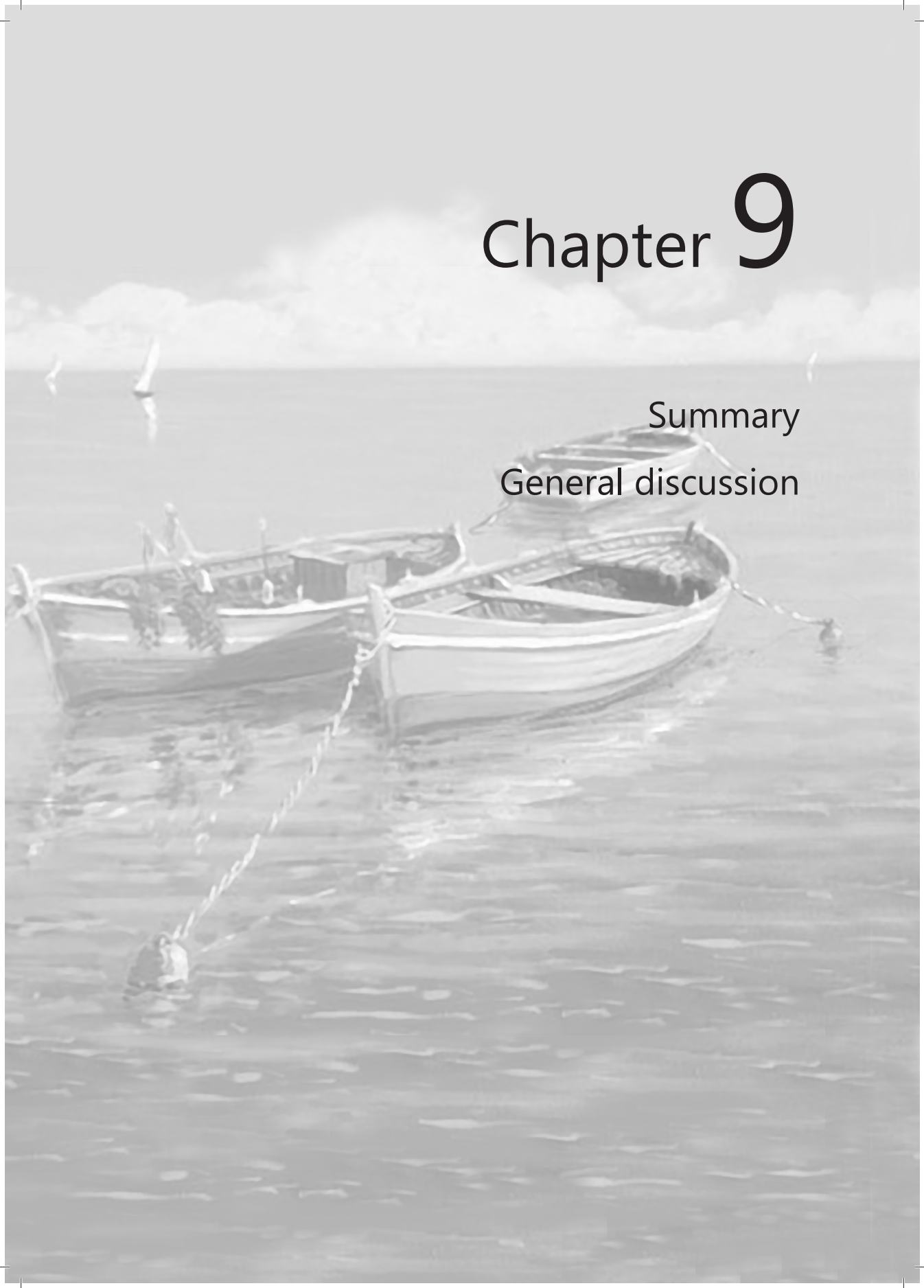

Chapter 9

Summary

General discussion

Summary

Sequencing both tumor and germline DNA is considered to be crucial for a better selection of patients for an appropriate anticancer therapy. As options for DNA analysis expand and costs decrease rapidly, more and more cancer patients are offered DNA testing in the context of personalized cancer treatment. Subsequently, these patients could face unsolicited findings, unintentionally discovered during the search for information that could improve antitumor treatment.

The research in this thesis focuses on the following research questions:

I. What are cancer patients' intentions, needs and preferences with regard to receiving (unsolicited) genetic information obtained by DNA sequencing and to sharing this information with their family members?
II. To what extent are these results confirmed in a larger group of cancer patients and do differences exist between patient subgroups?
III. What are important ethical considerations for a responsible DNA sequencing practice in clinical oncology?

In the first part of this thesis, we use qualitative research (semi-structured interviews) to investigate cancer patients' intentions, needs and preferences with regard to receiving genetic (risk) information obtained by DNA sequencing.

In **Chapter 2**, we describe our experience at The Center for Personalized Cancer Treatment (CPCT). The CPCT is a Dutch consortium, which offers centralized large-scale DNA sequencing for the discovery of somatic tumor mutations with their germline DNA as a reference. The aim of the CPCT is to give all cancer patients with advanced disease stage access to tumor DNA analysis in order to improve selection for experimental therapy and avoid unnecessary exposure to side effects. One of the challenges in daily practice is how to deal with unsolicited genetic germline findings, as this information may have potential medical, psychological, financial and social consequences for patients and their family members.
In Chapter 2 we describe three patients faced with an unsolicited finding while they intended to be a candidate for future anticancer treatment by participating in a trial that included DNA sequencing of both tumor and germline DNA. These three cases serve as an example to discuss ethical and organizational considerations regarding the management of unsolicited findings in personalized cancer research and treatment.
We recommend that unsolicited genetic research findings must first be confirmed by a validated test and patients should by counseled by a clinical geneticist or genetic counselor. Furthermore, we conclude that informed consent procedures need to be more explicit in asking patients if they want to be informed about unsolicited findings and what genetic risk information exactly they want to receive.

In **Chapter 3** we describe our qualitative study conducted with a group of 24 Dutch cancer patients with different types of cancer (both curative and advanced-stage cancer) who were invited to participate in our in-depth, semi-structured interviews to learn their intentions, needs and preferences with regard to receiving unsolicited findings obtained by DNA sequencing.
At the start of the interviews, almost all participants had a positive attitude about receiving unsolicited findings. This attitude changed after they were provided with more background information on DNA sequencing and with a model of four categories of unsolicited findings. During the interview, participants became more conservative and indicated that they preferred limiting the information they received to one or more variants of the four categories of genetic test results that were presented to them. The main concern of our participants was their own and others' (including family members) ability to cope with (the increased risk of having) a genetic disorder.
Hence, we conclude that providing background information gives cancer patients the opportunity to select subsets of unsolicited findings and increases their ability to make an informed choice. Special attention is needed for social and emotional factors to support patients themselves and when communicating unsolicited test results to their family members.

In **Chapter 4** we describe the next step of our qualitative research, namely, analyzing the interviews using the constant comparative method to develop codes and themes. This contributes to a better understanding of what cancer patients consider important and what influences them when making decisions about the disclosure of unsolicited findings of DNA sequencing.
Four interrelated themes emerged from our data: cancer patients felt a strong need to control their lives; they mentioned the importance of family dynamics; they experienced the DNA sequencing procedure regarding unsolicited findings as cognitively complex; and they also found it to be an emotionally complex process.
In Chapter 4 we show that using Joel Feinberg's classification of autonomy may help to better understand cancer patients' desire for autonomous decisions making, while also acknowledging the emotional and cognitive complexities of the disclosure of unsolicited findings.
Hence, understanding what a cancer patient could experience during the process of disclosing unsolicited findings from DNA sequencing will help oncologists in daily practice support patients in making informed decisions. For example, in dealing with the several layers of complexity of a sequencing procedure, conditions such as no time pressure for decisions, education, personalized counseling, and guidance are vital. Clinicians, in particular clinical geneticists, can support cancer patients with family dynamics by assisting their communication with family members and offering guidance when dealing with stressful

results. In Chapter 4, table 2, we summarize our findings and the practical implications of four dimensions of autonomy, according to Feinberg. These insights could be helpful for clinicians guiding patients through this complex process.

In the second part of this thesis, we use quantitative research (a structured questionnaire) to verify whether and to what extent the results of our qualitative research are confirmed in a larger group of cancer patients and if differences exists between patient subgroups toward receiving genetic (risk) information obtained by DNA sequencing.

In **Chapter 5** we describe the results of our quantitative multi-center study with adult cancer patients to understand their preferences concerning unsolicited findings and to study their wish for sharing this information with family members. Participants were surveyed through a digital questionnaire based on previous semi-structured interviews.
Our study showed that a vast majority (85.1%) of our participants preferred to receive unsolicited findings 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 participants would also opt for feedback of findings that currently are considered to be non-actionable. Nevertheless, there is also a substantial group (20.6%) of participants who did not wish to be informed about these so called non-actionable unsolicited findings. The same is true for variants of unknown significance (18.2%).
Statistically significant more men than women choose to receive unsolicited findings, especially regarding the non-actionable unsolicited findings (OR 3.32; 95% CI 2.05 - 5.37) and unsolicited findings of unknown significance (OR 2.00; 95% CI 1.25 - 3.21). Higher educational level was associated with higher preference of receiving actionable unsolicited findings (OR 2.31; 95% CI 1.02 - 5.22) and lower preferences for receiving unsolicited findings of unknown significance (OR 0.59; 95% CI 0.41 - 0.85).
Participants with living first or second-degree family members were more interested in receiving unsolicited findings of reproductive significance. For participants with children this finding was statistically significant (OR 5.05; 95% CI 2.97 - 8.58). Participants with religious conviction turned out to be less willing to receive information of non-actionable unsolicited findings (OR 0.54; 95% CI 0.38 - 0.79) than participants without religious conviction. For cancer subtypes, only participants with urogenital cancer had different preferences, e.g. less willingness to receive non-actionable unsolicited findings (OR 0.47; 95% CI 0.22 - 0.99) and unsolicited findings of unknown significance (OR 0.40; 95% CI 0.19 - 0.83).
It is remarkable that the interest in learning about the different categories of unsolicited findings is equally high among curative and advanced-stage patients.
These results provide oncologists with tools for a personalized approach to informed consent. We recommend incorporation of the four categories in informed consent

procedures to support patients in making informed decisions on unsolicited findings. A binning approach to unsolicited findings allows patients to accept, for example, actionable findings and at the same time to refuse non-actionable or uncertain findings. Binning also helps an important minority of patients who do not wish to know everything. Especially women would benefit from differentiating between categories of unsolicited findings.
Thirty three percent (n=244) of the participants wanted family members to have access to their unsolicited findings while still alive. After passing away, eighty-two percent (n=603) of the participants would agree to information being shared with relatives.
The majority of participants opposes the hospital contacting relatives directly to inform them about unsolicited findings, indicating that most patients want to act as a gateway between professionals and the patient's family. 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.

In the last part of this thesis, we discuss several ethical aspects considered to be important for responsible DNA sequencing practice in clinical oncology.

The question of who is responsible for conveying unsolicited findings to family members has become increasingly urgent now that DNA sequencing is finding its way into clinical practice. Although patients are aware that it is important to inform family members and they are generally willing to do so, this vital transfer of information often fails to occur. In **Chapter 6** we discuss the question of whose responsibility it is to convey relevant genetic risk information concerning hereditary diseases that can be cured or prevented in the relatives of patients undergoing DNA sequencing. We argue in favor of a shared responsibility for professionals and patients to warn relatives that are at risk. We present a strategy that reconciles these roles: a moral accountability nudge, grounded in the framework of libertarian paternalism. This nudge (to steer people's behavior in a direction that promotes the wellbeing of others) aims to create awareness on specific patient responsibilities and must be incorporated into the informed consent procedure and into counseling services, such as information letters and online tools.

In **Chapter 7** we present an ethical review on the question of whether healthcare professionals have a duty to screen genome sequencing data to check for life-threatening mutations or should instead focus on the primary reason for testing, namely achieving a personalized cancer treatment. We discuss the ethical arguments for and against routine screening of sequencing data (see also Chapter 7, Table 1: Debating routine screening of genomic testing data). Unless future research shows that routine screening is detrimental for patient health, or for affordable and accessible care, routine screening might be allowed to constitute a part of an ethically responsible sequencing workflow. Finally we propose that

routine screening in the clinic should, at least initially, be limited to life-saving findings so as to avoid overburdening the healthcare system with unexpected costs.

In **Chapter 8** we discuss the following question: should patients be free to decide themselves whether they want to receive genetic results? In other words, *must* genetic information be disclosed, even when patients have indicated that they do not to want to receive this information?
We explain why any genetic disclosure policy that works with defaults should be grounded in the framework of libertarian paternalism to assist people in making decisions regarding the wide array of complex genetic information should *always* be paired with an opt out. Packages of genetic information that patients do not want to receive should therefore not be analyzed at all, if possible.

General discussion

General discussion

In this era of precision medicine, genetic information is becoming abundantly available. Introduction of DNA sequencing in the field of clinical oncology promises to increase opportunities for tailored cancer treatment. This powerful tool provides solicited and unsolicited germline findings. Hence, cancer patients are more and more confronted with the possibility of encountering unsolicited findings, as a byproduct of a research question. This genetic risk information, inevitably generated, may have potential medical, psychological, financial and social consequences.
The general aim of this thesis was to examine cancer patients' intentions, needs and preferences with regard to receiving unsolicited genetic risk information obtained by sequencing and sharing this information with their family members.
In the first part of this thesis, we investigated in a qualitative study the intentions, needs and preferences of cancer patients with regard to receiving unsolicited genetic information and sharing this information with their family members. In the second part of this thesis, we used quantitative research to investigate whether these results are confirmed in a larger group of cancer patients and if differences exist between patient subgroups. In the third part of this thesis, we focused on determining what the important ethical considerations are for a responsible Next Generation Sequencing (NGS) practice in clinical oncology.
In this chapter, we answer the three research questions, we describe the limitations and clinical implications of our studies and we discuss future perspectives with regard to the return of unsolicited findings.

What are cancer patients' intentions, needs and preferences toward receiving (unsolicited) genetic information obtained by NGS and sharing this information with their family members?

In Chapter 3, describing our qualitative in-depth interview study, we show that almost all our participants, regardless of cancer diagnosis and tumor stage, would like to receive unsolicited findings. Participants were curious to find out what kind of diseases could be expected, what treatment options would be applicable, what the chances were of specific diseases, when that disease could appear and whether preventive measures could be taken. This positive attitude is consistent with recent literature showing that the return of unsolicited findings obtained from sequencing techniques is desirable. [1,2]
Cancer patients' need to control their lives is one of the four themes we discovered from our data using the constant comparative method as described in Chapter 4 of this thesis. By giving participants more background information, including our binning model of four categories of unsolicited findings, they gain control over their decisions with regard to the return of unsolicited findings. Hence, participants changed their preferences from receiving

all information to receiving subsets of genetic information, which is in line with earlier research.[2,3,4]

As previously mentioned, adequate understanding of genomic testing requires a high level of genetic literacy.[5] Although our participants had a high educational level, the return of unsolicited findings was still considered to be complex, both cognitively and emotionally. The fact that providing results to patients may cause (psychological) harm has also been previously described as a key concern of genetic health care professionals.[6] In our in-depth interviews, the main concern of our participants was their own and others' (including family members) ability to cope with the possible increased risk of having a genetic disorder.

In line with our research described in Chapter 2, participants reported that to be able to share genetic risk information, there should be a possibility to have easy access to health care professionals (e.g. clinical geneticists), also in the future, when there is a need to re-contact, for example to obtain additional information on the discovered unsolicited findings. Based on the results of this qualitative research, we recommend that (specific sets of) genetic germline information should be disclosed and we propose to offer tailored information regarding NGS to support healthcare professionals in close collaboration with clinical geneticists in the education and counseling of their patients, for example regarding sharing and communicating the genetic risk information to their family members.

To what extent are these results confirmed in a larger group of cancer patients and do differences exist between patient subgroups?

In this thesis, we present the first study that describes the quantitative results of a large Dutch cancer patient group concerning their needs and preferences with regard to receiving genetic (risk) information obtained by DNA sequencing and having this information shared with their family members. Our study showed that, in general, 85% of participants are willing to receive unsolicited findings. The finding that a majority of patients would like to get feedback on genetic information is consistent with previous studies that were conducted in a general population.[4] Moreover, our results also correspond to preferences measured in a population of American stage IV cancer patients.[2]

Even though our study showed that a majority of patients would opt to receive all unsolicited findings, after presenting four categories of possible unsolicited findings, we found a difference between actionable and non-actionable information, namely more patients are interested in receiving the actionable information. A substantial minority of patients did not wish to know that they are at risk for non-treatable hereditary conditions. Especially women would benefit from a differentiation between categories of unsolicited findings.

The importance of addressing the possibility of unsolicited findings in the informed consent procedure has previously been underscored in the literature, and also by our own group.[1,7,8]

Our quantitative study provides useful insights into how to shape such an "anticipate and communicate" approach.[9,10]
We suggest a tiered informed consent, offering predefined packages of unsolicited findings that can be used with options for patients to 'opt in' and 'opt out' for the return of unsolicited genetic results.
Since unsolicited findings can have large impact on patients and their family members, choosing to receive unsolicited findings due to a sequencing procedure should be an informed decision in clinical oncology.

What are important ethical considerations for a responsible NGS practice in clinical oncology?

During our research we encountered several topics that need to be addressed in the upcoming era of DNA sequencing.
We are convinced that health care professionals have the responsibility to offer patients the option to be notified of findings that potentially affect their own (and family members') health or may prevent significant harm. In Chapter 6, we describe the debate on the question of whether healthcare professionals have a duty to warn, not only their patients but also the patients' relatives. We argue that as the patient herself is an essential link between the professional and her relatives, the professional needs to support the patient to fulfill her duty to warn. We propose a libertarian benevolence strategy; it is a strategy to influence people's behavior in a non-coercive way, a nudge toward disclosure.[11] By making the patient aware of this special responsibility with regard to unsolicited findings and by stressing importance, the patient can be nudged in the right direction.
Beside the duty to warn, healthcare professionals are confronted with the question of whether it is their duty to hunt for pathogenic mutations throughout the whole genome sequencing data as new mutations became available in the research context. We argue that in the future, at least initially, routine screening in the clinic should be limited to life-saving findings.
Whether it is appropriate to re-contact patients, or contact their family members if the patient has passed away, is a topic of debate. The majority of our participants stated that they would not want the hospital directly contacting relatives to inform them about unsolicited findings. This indicates that most patients want to act as a gateway between professionals and the patient's family. Previous studies that elucidated patient preferences in a medical genetics clinic showed mixed results regarding family disclosure.[12] However, after passing away, the majority of our participants would prefer the hospital to actively contact their family to provide the unsolicited findings to their family members. A policy that allows family members to retrieve unsolicited findings after the patient has passed away could draw substantial support among cancer patients.

Finally, we discuss the current classic informed consent. Although most of our participants are willing to receive unsolicited findings, about 10% of our participants do not want to receive these findings. Patients who do not want to receive their genetic risk information are currently not able to completely "opt out"; they either have to choose not to participate or to consent to receiving unsolicited findings. We recommend always allowing patients to opt out.

Limitations of studies presented

In the studies of this thesis, only cancer patients who have mastered the Dutch language participated. Participants were mainly Caucasian, highly educated and had an appropriate health literacy level**,** which possibly impedes the generalization of our findings to other cancer patient populations.

For most participants, receiving unsolicited findings was a hypothetical situation. This raises the question of whether they would act in the same way if they faced the decision to receive unsolicited findings in real life.

We made an effort to offer information as comprehensibly as possible (like showing videos with background information and providing written information). Despite this support, and notwithstanding the fact that our participants had a high educational level, it became clear during the qualitative and quantitative studies that the return of unsolicited findings is a complex topic, both cognitively and emotionally.

Although we tried to formulate the background information on the impact of unsolicited findings as neutrally as possible, this formulation may have influenced the preferences that were measured.

Furthermore, it is well known that empirical research participants might be highly motivated to learn results, hence our participants might have been more interested in DNA sequencing than cancer patients in general.

Practical implications in clinical oncology

Studies in this thesis show that education and counseling are vital to enable cancer patients to make informed decisions. Even for highly educated people, this topic is rather difficult to understand. Thus, to make an informed, autonomous decision with regard to the return of unsolicited findings, understandable, personalized and accessible information (written or digital) and educational material must be available to empower cancer patients and their family members.

Based on the findings of this research, we conclude that in the era of DNA sequencing the classical informed consent must be adapted. Informed consent procedures need to be more explicit in asking patients if they want to be informed about unsolicited findings and, if so, exactly what genetic risk information they want to receive. Using a binning approach allows patients to differentiate between different categories of unsolicited findings.

As genetic data may gain significance in the course of scientific progress, patients should also be asked during the informed consent procedure under which circumstances they want to be re-contacted (or have family members contacted, if the patient has passed away).
If detected, we recommend that the unsolicited genetic research finding must first be confirmed by a validated test and we recommend that patients should by counseled by a clinical geneticist or genetic counselor, for example to assist communication with family members.
Although most participants are willing to receive unsolicited findings, about 10% of our participants did not want to receive this information. Therefore, taking into account their autonomy and well-being, participants who do not want to receive their genetic risk information should be offered an option to "opt out" and therefore should to be able to choose not to receive unsolicited findings.
In this thesis we emphasize that the professional and the patient share a responsibility to notify patients' family members. We therefore recommend using a moral accountability nudge (to steer people's behavior in a direction that promotes the wellbeing of others) during an informed consent procedure.
In conclusion, the disclosure policy we recommend contains a generic informed consent with default packages and the option to 'opt out'. The option of re-contacting patients and family members in the future, taking into account that the patient may have passed away, should be addressed during the informed consent procedure, as well as the responsibility to share actionable information.
Until this is realized, we recommend that packages of genetic information that patients do not want to receive should not be analyzed at all, even though we are aware of the difficulties this may pose for healthcare professionals.

Future directions

In the end, our four categories model could be refined. Before starting a sequencing procedure, patients should be able to learn what kind of diseases they could receive information about, what treatment options may be available for those diseases, what the exact chances are of getting those specific diseases, when the disease could appear and whether preventive measures could be taken.
In this thesis, both in the qualitative and quantitative studies we conducted, participants had a high educational level. Despite this, they experienced the return of unsolicited findings to be a complex process, not only emotionally, but also cognitively. If highly educated patients find this to be a complex process, it will certainly seem complex for more vulnerable patient groups, for example those with a low educational level or an inadequate health literacy. This raises questions about how these groups can best be protected. Appropriate supporting strategies need to be developed.
Another vulnerable group of patients are those who are diagnosed with childhood cancer. If sequencing techniques reveal unsolicited findings in children, when, to who and by whom

should this unsolicited information be returned? For this patient group as well, information concerning their and their parents' needs and preferences is required.
In our study, cancer patients stated that they would like the hospital to actively approach relatives to disclose findings after the patient's death. It is yet to be determined if this is possible and what kind of (IT) system could be used. The introduction of an independent, confidential officer should be considered. This independent officer would be in charge during the informed consent procedure and afterwards would be tasked with related issues, i.e. communication upon a family member's request and re-contact issues, for example after a patient's death.
Hence, in clinical oncology, the right question for professionals may not be whether to provide access to genomic information, but how to provide an adequate informed consent procedure and how to support patients who wish to receive unsolicited findings.

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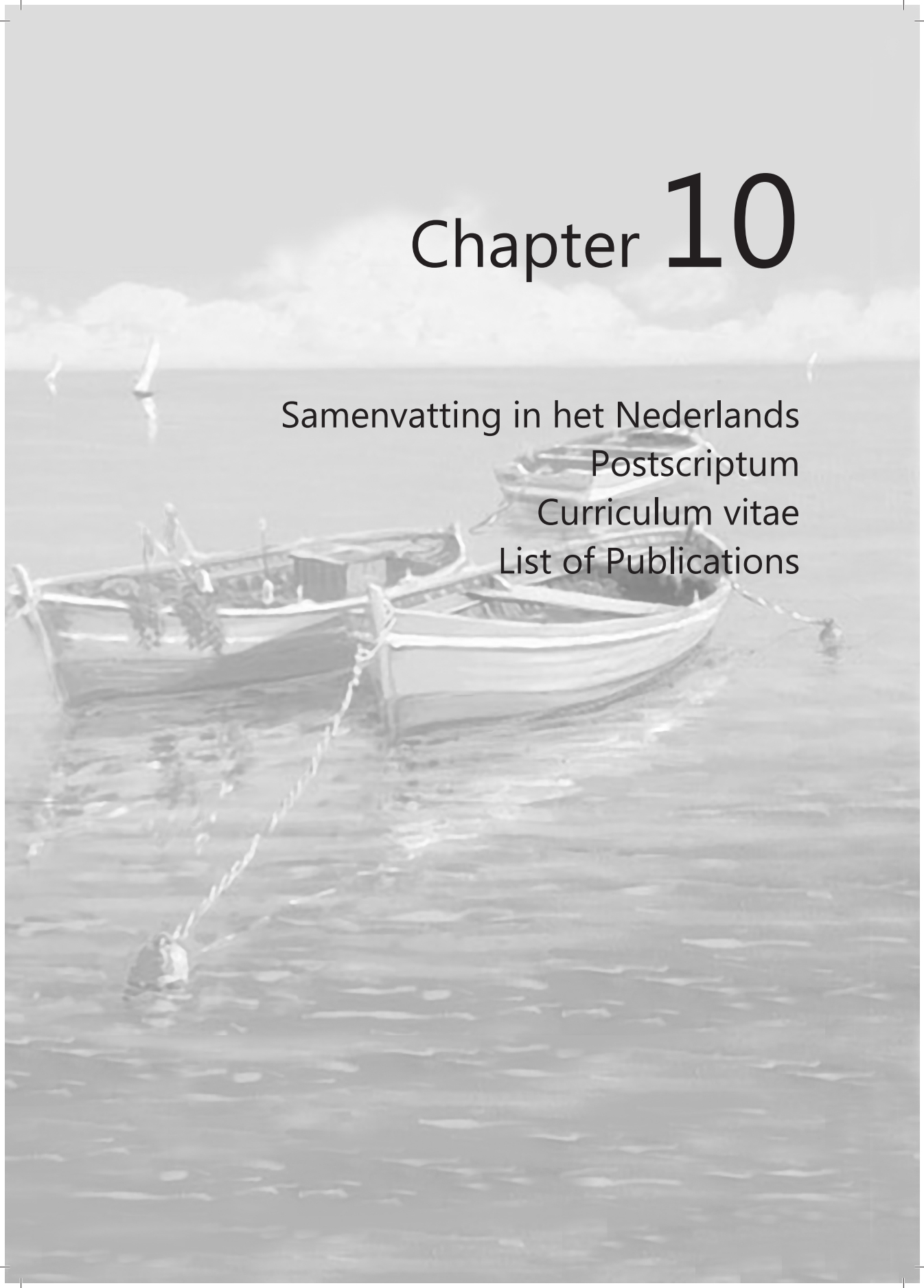

Chapter 10

Samenvatting in het Nederlands
Postscriptum
Curriculum vitae
List of Publications

Samenvatting in het Nederlands

Sequencing van zowel tumor- als kiembaan-DNA wordt als noodzakelijk beschouwd voor een betere selectie van patiënten voor een geschikte antitumorbehandeling. Naarmate de mogelijkheden van DNA-analyse toenemen en de kosten hiervan snel dalen, wordt in de context van *personalized medicine* aan steeds meer patiënten met kanker deze DNA sequencing techniek aangeboden.
Het gevolg van deze toename van DNA sequencing bij patiënten met kanker is dat er toenemend een mogelijkheid is dat deze patiënten geconfronteerd worden met onverwachte genetische bevindingen, de zogenaamde *genetische bijvangst*. Dit is genetische informatie die onbedoeld ontdekt wordt als bijproduct van een oorspronkelijke onderzoeksvraag, namelijk de zoektocht naar een betere selectie voor een antitumorbehandeling.

Het onderzoek in dit proefschrift richt zich op de volgende onderzoeksvragen:
I. Wat zijn de intenties, behoeften en voorkeuren van patiënten met kanker ten aanzien van het ontvangen van (onverwachte) genetische informatie verkregen middels DNA sequencing en het delen van deze informatie met hun familieleden?
II. Worden deze resultaten bevestigd in een grotere groep patiënten met diagnose kanker? Zo ja, in welke mate en zijn er verschillen tussen patiënten subgroepen?
III. Wat zijn belangrijke ethische overwegingen bij het op verantwoorde wijze invoeren van DNA sequencing in de klinische oncologie?

In het eerste deel van dit proefschrift maken we gebruik van kwalitatief onderzoek (semigestructureerde interviews) om te onderzoeken wat de intenties, behoeften en voorkeuren van patiënten met kanker zijn ten aanzien van het ontvangen van onverwachte genetische (risico) informatie verkregen middels DNA sequencing.

In **hoofdstuk 2** beschrijven we ervaringen van het Center for Personalized Cancer Treatment (CPCT). Het CPCT is een Nederlands consortium, dat gecentraliseerd grootschalig DNA sequencing aanbiedt voor het zoeken naar somatische tumormutaties met kiembaan-DNA als referentie. Doel van het CPCT is om alle patiënten met kanker in een gevorderd ziektestadium toegang te geven tot tumor-DNA-analyse om selectie voor een experimentele antitumor therapie te verbeteren en onnodige blootstelling aan bijwerkingen te voorkomen. Eén van de uitdagingen in de dagelijkse praktijk is om verantwoord om te gaan met onverwachte genetische bevindingen, omdat deze informatie mogelijk medische, psychologische, financiële en sociale gevolgen kan hebben voor patiënten en hun familieleden.
In hoofdstuk 2 beschrijven we drie patiënten die werden geconfronteerd met een onverwachte bevinding. Deze bevinding werd ontdekt bij DNA sequencing in het kader van screening voor een experimentele antitumor therapie. Deze casuïstiek wordt gebruikt als

voorbeeld om ethische en organisatorische overwegingen voortkomend uit deze onverwachte bevindingen te bespreken.
We benadrukken in dit hoofdstuk dat onverwachte bevindingen gevonden in een research context eerst moeten worden bevestigd middels een gevalideerde test in een gecertificeerd laboratorium en dat patiënten vervolgens een klinisch geneticus of een genetisch counselor zouden moeten raadplegen. We concluderen daarnaast dat tijdens informed consent procedures expliciet aan patiënten moet worden gevraagd of ze geïnformeerd willen worden over onverwachte genetische bevindingen en zo ja, welke genetische risico-informatie zij precies willen terugontvangen.

In **hoofdstuk 3** beschrijven we de eerste stap van ons kwalitatief onderzoek. Bij dit onderzoek werd een groep van 24 Nederlandse patiënten met verschillende soorten kanker (zowel curatieve als palliatieve fase) uitgenodigd om deel te nemen aan semigestructureerde interviews om hun intenties, behoeften en voorkeuren voor het ontvangen van onverwachte bevindingen verkregen middels DNA sequencing te onderzoeken.
Aan het begin van de interviews hadden bijna alle deelnemers een positieve houding ten opzichte van het ontvangen van onverwachte bevindingen. Dit veranderde na het verstrekken van meer achtergrondinformatie over DNA sequencing en na het aanbieden van informatie over mogelijke onverwachte bevindingen onderverdeeld in vier verschillende categorieën. Tijdens het interview werden de deelnemers terughoudender en gaven ze aan dat ze de voorkeur gaven aan een beperkte terugrapportage van één of meer varianten van de vier categorieën die aan hen werden gepresenteerd. De belangrijkste zorg van onze deelnemers was of zijzelf en anderen (inclusief familieleden) het vermogen zouden hebben om te kunnen omgaan met informatie over (het risico op) het hebben van een genetische afwijking.
We concluderen in hoofdstuk 3 dat het geven van achtergrondinformatie de mogelijkheid biedt aan patiënten met kanker om subsets van onverwachte bevindingen te selecteren, wat hun vermogen om een geïnformeerde keuze te maken verhoogt. Speciale aandacht is nodig voor sociale en emotionele factoren ter ondersteuning en begeleiding bij het communiceren van onverwachte genetische risico informatie naar familieleden.

In **hoofdstuk 4** beschrijven we de volgende stap van ons kwalitatief onderzoek, het analyseren van de interviews met behulp van de constant vergelijkende methode om codes en thema's te ontwikkelen. Dit draagt bij tot een beter begrip van wat patiënten met kanker belangrijk vinden en wat hen beïnvloedt bij het nemen van beslissingen over het al dan niet terug willen horen van onverwachte bevindingen ontdekt middels DNA sequencing. Vier onderling verbonden thema's komen uit ons onderzoek naar voren: patiënten met kanker hebben een sterke behoefte om controle uit te kunnen oefenen op hun leven; familiedynamiek speelt een rol; de DNA sequencing procedure met mogelijke onverwachte

bevindingen wordt als een cognitief complex en ook als een emotioneel complex proces beschouwd.
In hoofdstuk 4 laten we zien hoe het gebruik van de vier verschillende betekenissen van het begrip autonomie volgens Joel Feinberg kan helpen om de wens van patiënten met kanker voor autonome besluitvorming beter te begrijpen. Hierbij worden ook de emotionele en cognitieve vraagstukken met betrekking tot het bekend worden van onverwachte bevindingen geadresseerd.
In hoofdstuk 4, tabel 2 hebben we onze bevindingen en praktische consequenties van de vier dimensies van autonomie samengevat. Denk met betrekking tot de cognitieve en emotionele complexiteit van een sequencing procedure aan het introduceren van enkele randvoorwaarden tijdens de informed consent procedure vooraf aan een DNA sequencing. Bijvoorbeeld: geen tijdsdruk bij het nemen van beslissingen en de beschikbaarheid van goede informatievoorziening. Daarnaast is er na bekendwording van een onverwachte bevinding de mogelijkheid om te worden begeleid bij de communicatie hierover met familieleden en kan ondersteuning worden aangeboden om te leren omgaan met deze mogelijk stressvolle genetische risico informatie.
Kortom, inzicht in wat een patiënt met kanker zou kunnen ervaren tijdens het proces van DNA sequencing en het bekend worden van onverwachte bevindingen, zal in de dagelijkse praktijk helpen bij de begeleiding van patiënten tijdens een DNA sequencing procedure.

In het tweede deel van dit proefschrift gebruiken we kwantitatief onderzoek (een gestructureerde vragenlijst) om na te gaan of en in welke mate de resultaten van ons kwalitatief onderzoek worden bevestigd en om na te gaan of er verschillen bestaan tussen subgroepen van patiënten met kanker met betrekking tot het ontvangen van genetische (risico) informatie verkregen middels DNA sequencing.

In **hoofdstuk 5** beschrijven we de resultaten van onze kwantitatieve multicenter studie met volwassen patiënten met kanker. Deelnemers werden bevraagd via een digitale vragenlijst op basis van eerder afgenomen semigestructureerde interviews.
Tijdens de vragenlijst werden onder andere vier verschillende categorieën van onverwachte bevindingen aan de deelnemers voorgelegd. De eerste categorie bestaat uit *actionable* bevindingen (genmutaties die de patiënt predisponeren voor aandoeningen die te voorkomen of te behandelen zijn). De tweede categorie bestaat uit *non-actionable* bevindingen (genmutaties die de patiënt predisponeren voor aandoeningen die (nog) niet te voorkomen of te behandelen zijn). De derde categorie zijn onverwachte bevindingen die geen directe gevolgen hebben voor de gezondheid van de patiënt zelf, maar wel belangrijk kunnen zijn voor familieleden of (toekomstig) nageslacht. Tot slot de vierde categorie die bestaat uit onverwachte bevindingen van onbekende betekenis (genetische varianten waarvan de betekenis (nog) onduidelijk is).

In totaal hebben 1072 patiënten zich aangemeld, 845 deelnemers begonnen aan de vragenlijst en 701 deelnemers vulden de vragenlijst compleet in.
Onze studie toonde aan dat overgrote meerderheid (85,1%) van patiënten de voorkeur geeft aan het zo volledig mogelijk ontvangen van onverwachte bevindingen. Vrijwel alle deelnemers wensten de informatie die aanleiding geeft tot preventieve of therapeutische opties terug te horen en informatie over genetische afwijkingen die recessieve aandoeningen veroorzaken.
Een meerderheid (72,4%) van de deelnemers zou ook kiezen voor terugrapportage van bevindingen die op dit moment als *non-actionable* worden beschouwd. Niettemin is er ook een substantiële groep (20,6%) van de deelnemers die niet wenst geïnformeerd te worden over *non-actionable* onverwachte bevindingen. Hetzelfde geldt voor varianten van onbekende betekenis (18,2%).
Statistisch significant meer mannen dan vrouwen gaven aan onverwachte bevindingen te willen ontvangen vooral met betrekking tot de *non-actionable* onverwachte bevindingen (OR 3.32, 95% CI 2.05 - 5.37) en onverwachte bevindingen van onbekende betekenis (OF 2.00, 95% BI 1.25 - 3.21).
Hoger opleidingsniveau ging gepaard met een hogere voorkeur voor het ontvangen van *actionable* onverwachte bevindingen (OR 2.31; 95% CI 1.02 - 5.22) en minder voorkeur voor het ontvangen van onverwachte bevindingen van onbekende betekenis (OR 0.59; 95% BI 0.41 - 0.85).
Deelnemers met levende eerste of tweedegraads familieleden waren meer geïnteresseerd in het ontvangen van onverwachte bevindingen van reproductieve betekenis. Voor deelnemers met eigen kinderen was deze bevinding statistisch significant (OR 5,05; 95% BI 2,97 - 8,58).
Deelnemers met een geloof bleken minder bereid om informatie te ontvangen over *non-actionable* onverwachte bevindingen (OR 0.54; 95% CI 0.38 - 0.79) dan niet-gelovende deelnemers. Kijkend naar kanker subtype hadden alleen deelnemers met een urogenitale vorm van kanker andere voorkeuren, zij zijn bijvoorbeeld minder bereid om de *non-actionable* onverwachte bevindingen te ontvangen (OR 0,47; 95% CI 0,22-0,99) en de onverwachte bevindingen van onbekende significantie (OR 0,40; 95% CI 0,19 - 0,83)). Het is opmerkelijk te noemen dat de belangstelling voor de verschillende categorieën van onverwachte bevindingen even hoog is tussen curatieve en palliatieve patiënten.
Drieëndertig procent (n = 244) van de deelnemers wilde dat familieleden toegang hadden tot hun onverwachte bevindingen terwijl zijzelf nog in leven zijn. Na hun overlijden zou tweeëntachtig procent (n = 603) van de deelnemers ermee instemmen dat deze informatie zou worden gedeeld met familieleden. Uit onze resultaten blijkt dat veel patiënten de bescherming van hun genetische privacy koesteren. De meerderheid van de deelnemers wenst niet dat het ziekenhuis rechtstreeks contact met hun familieleden opneemt om hen te informeren over onverwachte bevindingen zolang zij zelf nog in leven zijn, wat aangeeft dat de meeste patiënten willen fungeren als een poort tussen professionals en de familie van de patiënt.

Bovenstaande resultaten bieden oncologen handvatten voor een gepersonaliseerde benadering van geïnformeerde toestemming. Het opnemen van de vier categorieën onverwachte bevindingen in de informed consent procedure is nuttig om patiënten te ondersteunen bij het nemen van weloverwogen beslissingen over deze onverwachte bevindingen. Door deze benadering van categoriseren van onverwachte bevindingen kunnen patiënten bijvoorbeeld *actionable* bevindingen accepteren en tegelijkertijd *non-actionable* onverwachte bevindingen weigeren. Dit categoriseren, ook wel *binning* genoemd, helpt ook een belangrijke minderheid van patiënten die aangeeft niet alles willen weten. Vooral vrouwen zouden baat hebben bij het maken van onderscheid tussen categorieën onverwachte bevindingen.

In het laatste deel van dit proefschrift bespreken we enkele belangrijke ethische overwegingen betreffende het op verantwoorde wijze invoeren van DNA sequencing in de klinische oncologie.

De vraag wie verantwoordelijk is voor het rapporten van onverwachte bevindingen aan familieleden wordt urgenter nu DNA sequencing een weg vindt naar de klinische oncologische praktijk. Hoewel patiënten weten dat het belangrijk is om familieleden op de hoogte te stellen en zij in het algemeen bereid zijn om dit te doen, komt deze essentiële informatie vaak niet bij de familieleden terecht. In **hoofdstuk 6** bespreken we de vraag wiens verantwoordelijkheid het is om, als er uit sequencing onverwacht genetische risico-informatie naar voren komt, aan familieleden van patiënten deze informatie te melden. Dit betreft informatie, die mogelijk betrekking heeft op aanwezigheid van erfelijke aandoeningen die kunnen worden genezen of voorkomen. We pleiten voor een gedeelde verantwoordelijk-heid voor zorgprofessionals en patiënten.
In hoofdstuk 6 presenteren we een strategie die leidt tot deze gezamenlijke morele verantwoordelijkheid. Deze strategie, *nudge* of duwtje in de goede richting, richt zich op het bij de patiënt creëren van bewustzijn over zijn/haar specifieke verantwoordelijkheden. Deze bewustwording over het hebben van een morele verantwoordelijkheid moet worden benadrukt aan de patiënt tijdens een informed consent procedure en moet expliciet worden opgenomen in hulpmiddelen zoals informatiebrieven en online begeleidende tools.

In **hoofdstuk 7** bespreken we de vraag of beroepsbeoefenaren in de gezondheidszorg de morele plicht hebben om onderzoekgegevens verkregen via whole genome sequencing te screenen op levensbedreigende mutaties of dat zij zich enkel kunnen concentreren op de primaire reden voor het testen, namelijk een gepersonaliseerde antitumor behandeling mogelijk maken. We bespreken de ethische argumenten voor en tegen, samengevat in hoofdstuk 7, tabel 1. Ten slotte stellen we voor dat een routinematige screening in de kliniek, in ieder geval in vooralsnog beperkt moet blijven tot levensreddende en ziektevoorkomende (*actionable)* bevindingen om overbelasting van het gezondheidszorgsysteem door

onvoorziene kosten te voorkomen.

In **hoofdstuk 8** bespreken we de vraag: *moeten* patiënten vrijgelaten worden in het nemen van de beslissing om al dan niet onverwachte resultaten verkregen middels DNA sequencing te willen ontvangen? Of moet genetische informatie worden onthuld, zelfs wanneer een patiënt heeft aangegeven geen terugrapportage te wensen?
We beargumenteren in dit hoofdstuk waarom elk terugkoppelbeleid bij voorkeur werkt met *default packages,* zogenaamde voor-geformuleerde standaard keuzes. Op deze manier patiënten helpen bij het maken van een keuze door alvast verschillende pakketten met genetische bijvangst aan te bieden, komt voort uit het liberaal paternalisme.
Wij benadrukken in hoofdstuk 8 dat er bij een informed consent procedure in het kader van terugkoppeling van onverwachte genetische informatie altijd de mogelijkheid van een opt-out, een mogelijkheid om geen informatie te ontvangen, beschikbaar moet zijn. De specifieke genetische informatie die patiënten niet willen ontvangen, moet daarom, indien mogelijk, helemaal niet worden geanalyseerd.

Postscriptum

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Iedereen die een bijdrage heeft geleverd aan het tot stand komen van dit proefschrift wil ik heel hartelijk danken. Naast een proeve van wetenschappelijke bekwaamheid, blijkt een promotietraject ook te bestaan uit het inzetten van organisatie talent, een portie doorzettingsvermogen en een dosis relativeringsvermogen. Het onderzoek en de artikelen die hier uit voortkwamen heb ik samen met een enthousiaste en inspirerende groep onderzoekers mogen vorm gegeven. Ik kijk terug op een mooie, intensieve reis in de wereld van de wetenschap.

De belangrijkste plek in mijn dankwoord verdienen de patiënten. De patiënten die door ons geïnterviewd werden over onverwachte bevindingen, verkregen middels DNA sequencing en de meer dan 1070 patiënten die de moeite hebben genomen om te laten weten dat zij geïnteresseerd waren in deelname aan ons onderzoek en bereid waren hun tijd hieraan te besteden. Mijn diepe dankbaarheid en respect hebben zij op de eerste plaats verdiend.

Prof. dr. Bredenoord, lieve Annelien, zeer veel dank voor het vertrouwen dat je in mij hebt gesteld. Jouw begeleiding, je enthousiasme en de inspirerende bijeenkomsten maakten dit promotietraject tot een ware ontdekkingstocht. Dank ook voor af en toe een uitstapje buiten de oncologie, richting de ethiek en de politiek. Ik bewonder je werklust en tomeloze energie, de feilloze analyses en de passie voor je vak. Ook op social media ben je een voorbeeld, jij krijgt al je promovendi aan het twitteren!

Prof. dr. Voest, beste Emile, onze kennismaking begon al tijdens mijn opleiding tot internist-oncoloog. Later, als beginnend staflid, bood jij mij de mogelijkheid om te promoveren en bracht jij mij in contact met Annelien Bredenoord. Wat ik jaren had afgehouden werd waarheid. Ik startte onder jouw begeleiding met een promotietraject. Dank voor deze mogelijkheid. Ik leerde van jou “groot” te denken en op mijn (wetenschappelijk) doel afgaan. Bovenal was het fijn om in onze onderzoeksgroep een bondgenoot met klinische doktersblik te hebben voor als (af en toe) de ethici te overheersend werden. En wat ben ik verwend met een promotor die vanuit het Antoni van Leeuwenhoekziekenhuis altijd naar mij, in het UMC Utrecht, toekwam!

Dr. Wessels, lieve Hester, met veel bewondering heb ik jouw betrokkenheid en onvermoeide werklust mogen ervaren. Wat hebben we op deze reis veel meegemaakt. Ik koester onze momentjes samen aan de koffietafel in de Brink, de interviews die we met onze ‘vintage’ opname apparatuur vastlegden en de vele uren die we samen besteed hebben aan het maken van de vragenlijst. Jouw steun heeft mij enorm geholpen.

Dr. May, lieve Anne, dankzij jou ben ik de statistiek gaan waarderen en heeft SPSS een deel van zijn geheimen prijs gegeven. Dank voor je zinvolle commentaren op onze stukken, het

meedenken tijdens onze besprekingen en de epidemiologische begeleiding. Dank voor alle praktische adviezen en speciale dank voor de hulp bij de analyse van het laatste artikel. Dank dat jij, samen met Hester Wessels, mijn copromotor wil zijn.

Dr. Ausems, lieve Margreet, dank voor al jou vele raadgevingen en je kritische blik. Met dank aan jouw input lukte het telkens weer om het belang van de samenwerking met de klinisch genetica te benadrukken en dit onderzoek naar een hoger plan te tillen. Zo fijn dat je, hoe laat op de avond dan ook, altijd bereid was om nog even naar een stuk van mij te kijken.

De leden van de leescommissie, Prof. dr. J.J.M. van Delden, Prof. dr. V.V.A.M. Knoers, Dr. G.S. Sonke, Prof. dr. A. Tibben en Prof. dr. P.O. Witteveen wil ik heel hartelijk danken voor hun tijd en hun bereidheid dit manuscript inhoudelijk te beoordelen en te opponeren.

Drs. Wouters, beste Roel, promoveren doe je niet alleen. Vanaf jaar 2 kwam jij mee werken op ons KWF project. Ik heb je leren kennen als een heel gedreven onderzoeker. Dank voor je prachtige zinsconstructies, je scherpe blik en vooral de plezierige samenwerking. Onze dagelijkse emailwisseling in augustus 2018 zal ik niet snel vergeten, de eindstreep is bereikt!

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Het pre-testen van de interviews en de vragenlijsten door Peter Holleman, Monique Kleinjan en mevrouw van Soest was eveneens onmisbaar. Speciale dank ook aan Coby van Rijn van de receptie van het Juliuscentrum, die maandenlang de enveloppen met aanmeldingen voor onze OncoGenEthics studie in onze brievenbus legde en trouw mailde als er weer post was.

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De staf Medische Oncologie, Inge Baas, Lot Devriese, Eelke Gort, Gerard Groenewegen, Alexander de Graeff, Nadia Haj Mohammad, Miriam Koopman, Jeanine Roodhart, Britt Suelmann, Karijn Suijkerbuijk, Filip de Vos en Els Witteveen, dank ik hartelijk voor de tijd die ik aan mijn proefschrift kon besteden en het vertrouwen dat jullie mij hiermee gaven. Speciale dank aan Els Witteveen voor het mogen inplannen van schrijfweken en het op zich nemen van de taak van voorzitter van de leescommissie.

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geïmplementeerd, dit alles in nauwe samenwerking met de AYA's zelf. Dank voor jullie enthousiasme en de energie die ik steeds krijg van deze gezamenlijke initiatieven!

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Lieve Paranimf, lieve Joke Pietersma, onze eerste ontmoeting was op het schoolplein, allebei hoogzwanger van ons 3de kindje. Sindsdien lopen de levens van onze gezinnen parallel en hebben we vele momenten met elkaar doorgebracht. Een hechte Happy Family band is zo gevormd. Samen met Martin, Valerie, Louise en Josephine zijn we altijd in voor een (sportieve) activiteit, bijvoorbeeld op Ameland, in Zeeland of op de ski's in Oostenrijk. Of gewoon spontaan op vrijdagavond even bijkletsen, want dan kook ik! Lieve Joke, jouw warme persoonlijkheid en betrokkenheid zijn heel bijzonder en belangrijk voor mij. Ik ben dan ook heel blij dat jij naast mij staat op 9 januari. En ik zeg maar zo: Wvttk!

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Rhodé M. Bijlsma, november 2018

Curriculum Vitae

Curriculum Vitae

Rhodé Marie-Lise Bijlsma – van Leeuwen was born on October 25th, 1977 in Zeist, the Netherlands. She attended secondary school at the Christelijk Lyceum (Gymnasium) in Zeist. In 1997 she graduated from the University of Utrecht with her undergraduate degree in Law. She received her medical degree in 2004.

In 2004, she became a resident in Internal Medicine at Diakonessenhuis Utrecht (supervision dr. W. N. M. Hustinx). In 2007 she continued her residency in Internal Medicine at the University Medical Center of Utrecht (supervision Prof. dr. E. E. van der Wall) and started her second job in motherhood.

In 2008, she started her specialization in Medical Oncology under the supervision of Prof. dr. E.E. Voest. In 2011 she started working as a staff member in the Medical Oncology department of the University Medical Center of Utrecht. In 2014, during her work as an medical oncologist, she started her PhD project described in this thesis at the Department of Medical Oncology of the UMC Utrecht Cancer Center, supervised by Prof. dr. A.L. Bredenoord and Prof. dr. E.E. Voest. In 2015 their research project obtained a grant from the Dutch Cancer Society.

Rhodé Bijlsma is currently working as a Medical Oncologist with special expertise in breast cancer. She is closely involved with the National Adolescents and Young Adults (AYA) Platform. She is project leader of 'AYA, Young and Cancer' in the UMC Utrecht Cancer Center, where she established the AYA lounge, an e-learning program and founded an adolescents and young adult patient focus group.

Rhodé is very much involved in teaching medical students, for example in her role as leader of the third-year bachelor program "Healthy and Sick Cells". In 2017 she obtained her University Senior Teaching Qualification (SKO).

Rhodé is married to Ward Bijlsma. Together they have three children (Annelie 2007, Laurens 2008, Liselot 2012). Sailing and standing up paddling are their favorite holiday activities. Life's a beach!

List of publications

List of Publications

Bijlsma RM, Bredenoord AL, Gadellaa-Hooijdonk CG, Lolkema MP, Sleijfer S, Voest EE, Ausems MG, Steeghs N. Unsolicited findings of next-generation sequencing for tumor analysis within a Dutch consortium: clinical daily practice reconsidered.
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