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Zusammenfassung des wissenschaftlichen Inhalts

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Our innovative research findings, based on an empirical-ethical study, for the first time in international research were able to reveal that patients do not grasp future stratification in cancer treatment by means of a biomarker. These findings are highly relevant for the ensuring of an informed consent procedure in clinical genetic research projects.

Despite enormous progress in treatment, cancer is still one of the most feared diseases of our time. A good diagnostic and treatment consultation therefore requires high communication skills both on the part of the physician and of the patient. Therapeutic misconception is a well-known challenge for informed decision-making for cancer research participants. From an ethical and clinical perspective this continues to be a serious problem. What is still missing, is a detailed understanding of the impact of 'personalised' treatment research (e.g. biomarkers for stratification) on research participants. For this, within our sub-project 9 of the UMG's clinical research group (KFO 179/2), we conducted, the first longitudinal empirical-ethical study based on in-depth interviews with colorectal cancer patients (n=40). These patients were enrolled in biomarker research concerning (neo)adjuvant treatment response, in which context we analysed their understanding of and perspectives on research and treatment with qualitative methods.

Our findings provide insight into how cancer patients involved in personalised cancer research assess and (mis)interpret the information provided. We found misconception based on patients' confusion of research and treatment, and here triggered by misled motivation, information paternalism or incomprehension, we identified genetic misconception and genetic responsibility as new problematic issues.

Patients predominantly were not aware of the major research aim of future stratification into responders and non-responders nor did they fully acknowledge this as an essential aim of personalised cancer research. This shows that ethical and practical reflection on informed decision-making in cancer treatment and research needs to more strongly take into account the complexity of lay interpretations of modern personalised medicine. Further, given the detected low impact of written information, such as ICFs, the role of these documents should be critically assessed. Despite the high level of formal safeguarding of written consent forms through ethics committees, the actual practical consultations are not sufficiently examined or reflected on, constituting an ethical problem in the context of IC in clinical trial participation. Especially, if the content of the ICFs does not give patients the possibility of comprehensibly informing themselves, these must be altered and possibly combined with alternative strategies, entailing a more personalised communication approach to inform and motivate patients for cancer research.

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Why take part in personalised cancer research? Patients' genetic misconception, genetic responsibility and incomprehension of stratification—an empirical-ethical examination

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Therapeutic misconception is a well-known challenge for informed decision-making for cancer research participants. What is still missing, is a detailed understanding of the impact of “personalised” treatment research (e.g. biomarkers for stratification) on research participants. For this, we conducted the first longitudinal empirical-ethical study based on semi-structured interviews with colorectal cancer patients ($n = 40$) enrolled in a biomarker trial for (neo)adjuvant treatment, analysing the patients' understanding of and perspectives on research and treatment with qualitative methods. In addition to therapeutic misconception based on patients' confusion of research and treatment, and here triggered by misled motivation, information paternalism or incomprehension, we identified genetic misconception and genetic responsibility as new problematic issues. Patients mainly were not aware of the major research aim of future stratification into responders and non-responders nor did they fully acknowledge this as the aim for personalised cancer research. Thus, ethical and practical reflection on informed decision-making in cancer treatment and research should take into account the complexity of lay interpretations of modern personalised medicine. Instead of very formalistic, liability-oriented informed consent procedures, we suggest a more personalised communication approach to inform and motivate patients for cancer research.

KEYWORDS

biomarkers, clinical trials, colon cancer, ethics, genetics, patient information

1 | INTRODUCTION

Despite enormous progress in treatment, cancer is still one of the most feared diseases of our time (Stewart & Wild, 2014). A good diagnostic and treatment consultation therefore requires high communication skills both on the part of the physician and of the patient. Clinical guidelines help structure the content of such consultations (Furber, Bonas, Murtagh, & Thomas, 2015; Hall, Prochazka, & Fink, 2012; Weisz et al., 2007). The option of participation in clinical trial research, such as in biomarker research, complicates the informed consent (IC) and decision-making process. Information on diagnosis, treatment, and clinical trial must be

disclosed and understood according to the ethical-legal principle of IC. However, patients generally are insecure in conversations on cancer treatment and their information needs often change during the course of their disease (Jenkins, Fallowfield, & Saul, 2001). It has repeatedly been confirmed that especially in such situations patients are prone to *therapeutic misconception* (Appelbaum, Lidz, & Meisel, 1987a; Henderson et al., 2007; Miller & Joffe, 2006; Pentz et al., 2012); they cannot differentiate between the aim of the clinical trial and the actual treatment, as they mistakenly assume they themselves are provided with a better treatment as in “newer treatment” (Catania et al., 2014; Flory & Emanuel, 2004; Jenkins et al., 2011; Pentz et al., 2012).

Additionally, various misconceptions are identified in the context of genetics (McKusick, 1971). To date, the extent to which such misconceptions occur, in which particular form within biomarker research on the part of patients (e.g. regarding the purpose of a biomarker), has not been analysed sufficiently (McKusick, 1971; Nuffield Council on Bioethics, 2010).

From an ethical and clinical perspective this continues to be a serious problem. How can we appropriately enforce and ensure the patient's right to self-determination and IC and at the same time pursue necessary research in oncology? How do new paradigms such as "personalised" oncology generate new challenges in this context? To answer these questions, we took a closer look at clinical cancer research from the patients' perspective.

1.1 | Background: misleading motivation, information paternalism or incomprehension

Therapeutic misconception has multiple definitions (Henderson et al., 2007). However, it commonly entails the failure of grasping or unawareness of the difference between research and standard treatment which is essential to an informed and autonomous decision (Appelbaum, Roth, Lidz, Benson, & Winslade, 1987b; Burke, 2014). This form of misconception is reported to be high and, as Kim et al. (2014) emphasise, commonly occurs in oncology clinical trials. Therapeutic misconception can also entail confusion about the purpose of particular research by which patients see personal benefit connected to their participation in a clinical trial or attribute therapeutic intent to the research being conducted (Burke, 2014). Thus, when participants confuse the goals of clinical trials with medical care, they underestimate the risks and overestimate the benefits (Henderson et al., 2007; de Melo-Martín & Ho, 2008). Some studies have focused on the potential effect clinical trial participation may have on the outcome of treatment including health service and survival. However, only few studies have found an association between trial participation and better survival (e.g. Unger et al., 2014), other studies have referred to careful consideration of these findings or have found no clear evidence of such an effect (Chow et al., 2013; Peppercorn, Weeks, Cook, & Joffe, 2004; Selby & Autier, 2011; Tanai et al., 2009; Vist et al., 2005). Factors contributing to therapeutic misconception can include the patient's motivation for personal benefit, content of written IC forms of the clinical trial, and the patient's physician acting as a researcher (Dellson, Nilbert, Bendahl, Malmström, & Carlsson, 2011; Kim et al., 2014). With a wider conception of the problem of therapeutic misconception three major lines of argumentation can be differentiated.

First, *motivation* for research participation can be misleading. Patients make a moral commitment to take part in clinical research and this often leads to unrealistic expectations and misplaced trust. This aspect differs categorically from the cognitive and emotional levels of information processing. In the past, several authors have emphasised altruism and solidarity as major (appropriate) motives for research participation (Godskesen, Hansson, Nygren, Nordin, & Kihlbom, 2015; Godskesen, Nygren, Nordin, Hansson, & Kihlbom, 2013; Newington

& Metcalfe, 2014; Truong, Weeks, Cook, & Joffe, 2011). Such altruistic motivation comprises the wish to help others (e.g. future patients or to support medical progress). Therapeutic misconception indicates, however, that another misleading motivation exists—personal interest and the (unrealistic) hope for individual therapeutic benefit (Flory & Emanuel, 2004; Godskesen et al., 2013). The study by Townsley et al. (2006) revealed that patients also agree to research participation because they believe it is expected by their physicians. Further, the survey by Catania et al. (2014) found that the majority (85%) of interviewed patients believed their physicians involved them in clinical research trials (phase 1) only because of personal academic stakes. Patients confessed their fear to raise questions because they did not want to risk the "good" relationship between them and their physicians.

Second, a form of *information paternalism* by clinicians can also occur, presumably with the intention of protecting the patient. Having difficulties to assess what kind and amount of information patients need, physicians often decide based on their own, personal preferences (Aggarwal, Davies, & Sullivan, 2014; Bergenmar, Johansson, & Sharp, 2014; Furber et al., 2015; Jenkins et al., 2011). However, this does not always match the patients' needs and might conflict with ethical-legal requirements of a fully informed patient. Particular research contexts of third-party benefit are regarded as critical. Specifically genetic, biomarker or biobank research seems to have a tendency of providing a low level of information (Klitzman, 2010), as a current systematic analysis of IC material in Germany has revealed (Hirschberg, Knüppel, & Strech, 2013). This might also mirror the fact that long-term benefits and use of this type of research are often undetermined or remain vague.

Third, the problem of *incomprehension* or also low medical literacy exists on the patient's side. This is due not only to educational background but also due to having to deal with the enormous psychological burden. Especially in oncology research, in accordance with the stress and coping model, denial is used as an adaptive strategy to protect against overwhelming events and feelings (Vos & de Haes, 2007). Incomprehension in this context can be considered a part of denial, as a strategy to not have to deal with the "bad news" of a cancer diagnosis. Several studies have revealed that patients are often unaware of the fact that they are enrolled in studies or they cannot recall the clinical trial's aim (Appelbaum & Lidz, 2011; Mexas et al., 2014; Miller et al., 2013; Wendler & Grady, 2008). As Sanchini, Reni, Calori, Riva, and Reichlin (2014) showed, less than two-thirds of patients knew that they were research participants. Only 44% understood the clinical trial's procedure and only 40% could name at least one of the risks or complications related to research participation. The survey by Miller et al. (2013) supports this insight even more radically. They asked for self-assessment regarding the understanding of clinical trial information: only 10% of the patients felt they really understood the text. The question arises of how to deal with patients who due to denial cannot be sufficiently informed about the aims of clinical trials and their hopes for personal benefit connected to the research situation.

The three areas of challenges to physician-patient consultations show that cancer research in general, which aims at discovering more about the biology and susceptibility of cancer, tends to be difficult for lay people to understand due to complex content and complex

medical terminology (Chapman, Abraham, Jenkins, & Fallowfield, 2003; Pieterse, Jager, Smets, & Henselmans, 2013). What does this mean for the development of biomarker research, which aims at stratifying diseases into much finer groups? It is known that therapeutic misconception concerning genetics does occur within the context of clinical cancer trials (Klitzman, 2010). The introduction of “individualised” or “personalised” medicine with the potential feasibility of examining large parts of DNA with low costs and classifications such as so-called “non-responders” may create new challenges in the physician–patient communication process.

The broad field of biomarker research is growing rapidly due to the development of new technologies of whole genome sequencing. To date, few studies exist which address research participants’ understanding of possible side effects of modern biomarker research including non-response. Also little research has been done on how this understanding shapes patients’ expectations of being involved in biomarker research.

In the current situation, research ethics committees invest a lot of time and resources for “improving” IC materials (Hedgecoe, 2014; Hirschberg et al., 2013; Ilić, Auchlin, Hadengue, Wenger, & Hurst, 2013; Koyfman et al., 2013; Pollock, 2012). There is a general assumption that it creates greater trust in clinical research when many details are revealed (Henman, Butow, Brown, Boyle, & Tattersall, 2002; Sutrop, 2013). Whether this is always the case can, however, be questioned. What is still missing in the entire picture is a detailed understanding of the impact and dimension of so-called “individualised” or “personalised” treatment research on the participating patients. Here, we refer to biomarker research for better patient stratification into responders and non-responders to (neo)adjuvant treatment, a major aim of cancer biomarker research. To which extent are the three areas: motivation, information paternalism, and incomprehension accordingly modified?

2 | METHODS

2.1 | Procedure

We examined the motivation for participation in the clinical trial from the patients’ perspective. Our longitudinal empirical-ethical study consisted of a two-stage observation- and interview study (Institutional Ethical Approval was given for this study [no. 1/6/2011] by the Ethics Committee of Göttingen on 12 July, 2011). It took place in a broader framework of a leading German clinical research unit

[“Biological Basis of Individual Tumor Response in Patients with Rectal Cancer,” funded by the DFG (Deutsche Forschungsgemeinschaft – German Research Foundation) 2009–2014, 179/2]. The clinical research unit aims at developing and validating prognostic tests to, in the future, stratify colorectal cancer patients according to their response to (neo)adjuvant treatment (Rödel et al., 2012; Sprenger et al., 2010). The treatment scheme provided at this hospital was a phase II clinical trial and took place as presented below (Fig. 1). The respective hospital annually treats around 160–180 colorectal cancer patients.

2.2 | Participants

Overall, 40 colorectal cancer patients were included in our empirical-ethical study. Several physician–patient consultations ($n = 54$) were observed and up to three semi-structured interviews were conducted with each patient ($n = 93$) (Table 1). The participation in our empirical-ethical study was optional and independent of the clinical trial of the hospital presented above.

For the in-depth analysis of the information and of the communication process from the patients’ perspective, we laid a focus on those patients who gave three interviews within their treatment and then expanded the analysis to all patients included ($n = 40$).

Three of the 40 patients withdrew from our empirical-ethical study, one due to poor health conditions and the other two after the first interview without giving a reason. Further, 12 other patients were involved in less than three interviews as four passed away during treatment, four were treated at external hospitals, and another four had a shorter treatment regimen. Considering the socio-demographic characteristics of these 15 patients who dropped out of our sample, they were over proportionally male and in the dominant age group of 61–70. Other collected socio-demographic factors were not strongly affected by the reduced sample size (see Table 1 for further details, column *Drop-outs*). Further, the information provided by the patients who dropped out of our sample in the course of the interview study due to the reasons presented above did not alter the saturation of information achieved. Comparatively, this is a sound and large sample for a qualitative study.

2.3 | Data collection

First, we observed the initial clinical physician–patient consultation, which we documented by hand. In non-participatory observation,

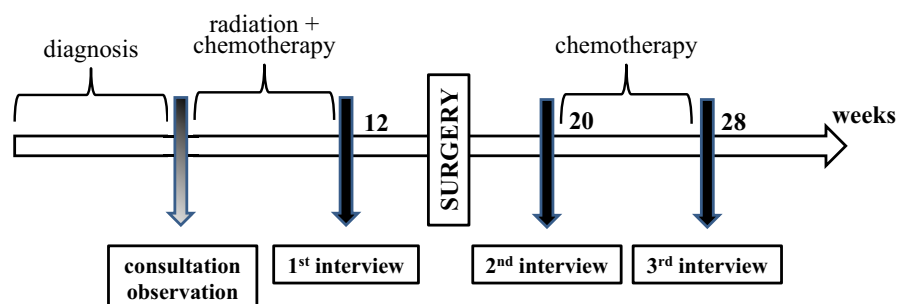


FIGURE 1 Treatment scheme and sequencing of data collection

TABLE 1 Socio-demographic data of the initial patient sample: $N = 40$, of the patient sample who gave three interviews: $n = 25$, and of those who dropped out of the sample: $n = 15$

Category	Specification	$N = 40$	$n = 25$	Drop-outs ^a
Gender	Female	14	10	-4
	Male	26	15	-11
Age	18-40	3	2	-1
	41-60	11	9	-2
	61-70	17	9	-8
	71-80	8	4	-4
	Over 80	1	1	
Educational background	No school-leaving qualification	1	1	
	Elementary school	11	4	-7
	Secondary school	24	16	-8
	University degree	4	4	
Family status	Single	2	1	-1
	Long-term relationship	3	2	-1
	Married	24	17	-7
	Divorced	5	2	-3
	Widowed	6	3	-3
Religious affiliation	Protestant	25	16	-9
	Catholic	8	7	-1
	No religious affiliation	7	2	-5

^aThese are the 15 patients who dropped out of our sample in the course of the study due to the reasons mentioned above in section 2.2 Participants.

proceedings and field notes are common elements (Hennink, Hutter, & Bailey, 2011). We used a structured sheet for the documentation of the consultations. At this hospital the surgeons and radiotherapists led these consultations. During the consultation, we witnessed the consent procedure where the patients also were provided with informed consent forms (ICFs), one for the respective treatment regimen and the clinical trial and one for blood and specimen samples. To ensure IC for our own empirical-ethical study, the physician gave a short introduction to our study in advance. Later, the physician gave a more detailed introduction before asking the patient whether he or she consented to having the consultation observed by us. If the patient agreed, we entered the consultation room and documented the respective consultation. This procedure was inevitable due to the tight schedule of the hospital and not wanting to delay the physician's IC consultation. Following the consultation, the patient was informed about our empirical-ethical study by one of our colleagues. The patients then had the possibility to consent to or decline participation in our empirical-ethical study. In the case of the latter, the written records were instantly destroyed. Second, we conducted a first semi-structured interview with each patient after on average 12 weeks of treatment before surgery. The second interview followed after on average 20 weeks of treatment after initial surgery recovery. The third and last interview was conducted after on average

28 weeks of treatment when chemotherapy was (almost) completed. Figure 1 also gives an overview of the timing and sequencing of data collection. All interviews were audio-recorded. The patients had to consent to each of the three interviews anew. Thus, the option of refusing an interview during their cancer treatment could be ensured.

2.4 | Data analysis

All material (Fig. 2) was analysed by means of content analysis (Mayring, 2007) assisted by the scientific software Atlas.ti™ by coding and then categorising statements in order to identify general lines of argumentation or topics (Fig. 3). Team coding was conducted to increase coding reliability (Green et al., 2007). We subsequently analysed all types of written and orally provided information regarding clinical trial participation. We focused on six basic codes for this analysis: (1) patients' knowledge of clinical trial, (2) patients' motivation for research participation, (3) patients' assessment of clinical trial, (4) patients' knowledge of personalised medicine, (5) patients' assessment of personalised medicine, and (6) patients' assessment of treatment and prognosis (see Table 2 for description of applied codes.). With these codes we then identified general patterns of motivation for and understanding of clinical trial participation.

For the systematic qualitative content analysis all material was pseudo-anonymised. First, the notes of the physician-patient consultations were transcribed and then imported into Atlas.ti™. Second, we analysed and compared these documentations with the two written ICFs (ICF 1 and ICF 2), which both included information on the treatment regimen and on the clinical trial participation and with the one written ICF (ICF 3) including information on blood and tissue samples, handed out to the patients during their first consultation at the hospital. Third, we transcribed the patients' audio-recorded interviews and also imported these into Atlas.ti™ for the analysis. During the analysis, the physicians' statements were compared with the patients' statements during consultation and later on in the interviews for detecting differences in understanding, misunderstanding, and gaps in recollection of issues. Here, we will use prime examples translated into English for exemplifying our findings. Notably, patients were not explicitly questioned about the content of the ICFs in the interviews; however, the answers to the questions of the semi-structured interviews provided information on the understanding and recollection of the content and the purpose of the clinical trial, thus the questions include scanning of the patients' state of knowledge (Table 3). The qualitative methodology setting is most appropriate to detect new issues and derive hypotheses.

3 | RESULTS

Our results can be divided into four main findings. They reveal three particular forms of motivation for clinical trial participation in the context of treatment of colorectal cancer—solidarity, genetic responsibility, and “personalised” benefit. Furthermore, our results indicate that patients do not understand the actual, major aim of the clinical trial they are participating in, namely, future stratification. In the following,

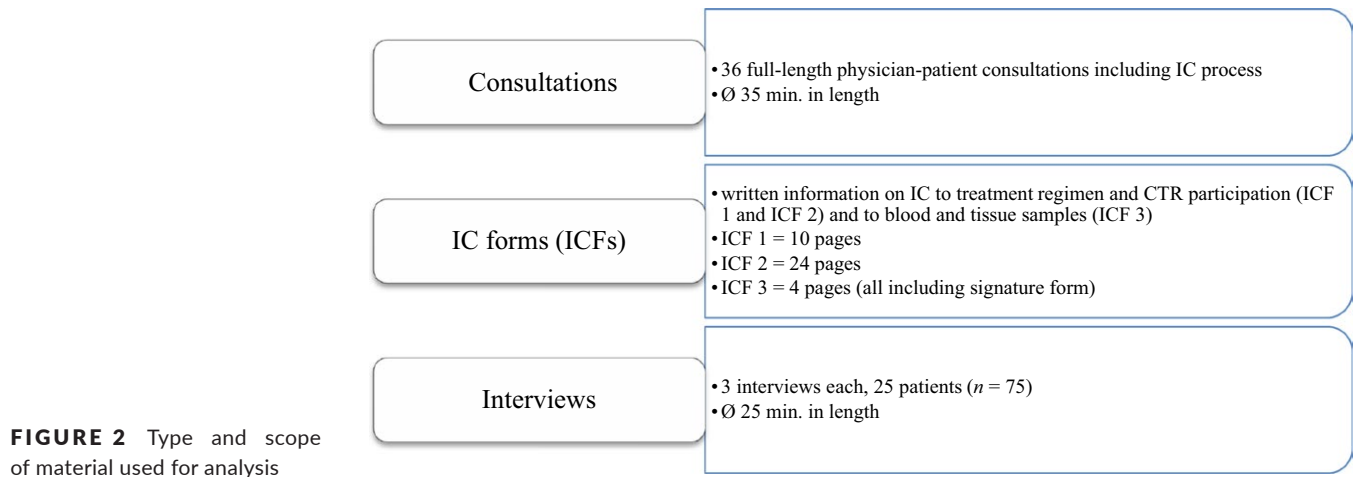


FIGURE 2 Type and scope of material used for analysis

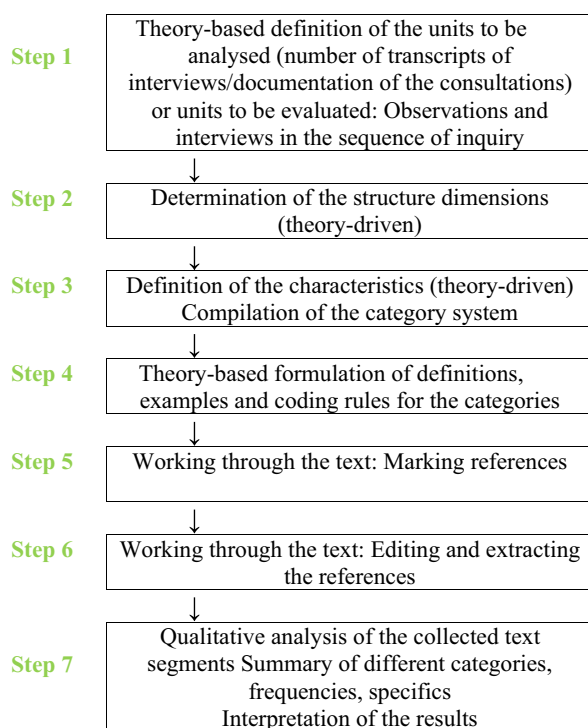


FIGURE 3 Procedure of our systematic qualitative content analysis (Mayring, 2007)

the findings are structured according to the three types of data to mirror the process of communication.

3.1 | Induced solidarity and social expectations as research participation motivation

Throughout the sample, the motivation for research participation is predominantly based on solidarity. Solidarity here entails the willingness to help others due to strong identification with other patients with the same illness. It is here based on social reciprocity, a medical-culturally developed principle. It is partially triggered by wording of the physicians and wording in the ICFs. Such wording includes “patients like you,” “help

other people,” “future treatment improvement.” It is also seen as socially desirable, as patients are motivated to please the physician.

In contrast, very few statements were found supporting true altruism, which is commonly claimed to be a factor in motivation. We find altruism differs from solidarity in its originating motivation (see discussion).

The consultations with the treating physician include wording referring to future patients who can profit from participation in research, because treatment will be improved. The aim indicated is the future of an optimised treatment, by for example, altering the amount of radiation on the basis of biomarkers.

Dr. AB: [...] If you consent to participate in the clinical trial, you would encounter no disadvantages as a consequence. With this you might help other people in the future, who then can be treated more optimally.

Also the ICFs use solidarity for motivating patients by referring to “patients with the same illness” (ICF 1, p. 4; ICF 2, p. 7; ICF 3, p. 1) and with

[...] This research solely serves scientific progress and a future treatment optimisation. (ICF 1, p. 3)

Our analysis of the interviews revealed that the statements towards indicating “solidarity as social identification” strongly resembled statements made in earlier consultations. They also included references to “future patients,” “same illness,” and “better treatment.” Another form of solidarity was linked to social reciprocity; it comprises the line of argumentation that patients before them have done their part and now it is their turn to do the same. Only two patients mention altruism as a form of motivation for research participation; these patients express the wish to serve the general public and stress their ideal of not being egocentric.

Mr. 18 B, 1st interview: Ahm, I expect the following from this. Ahm, I myself can profit from other people who have endured this before me [...]. And my data will also be used for future people.

Interestingly, altruism could not be found either in the statements during the consultations or in the ICFs.

TABLE 2 Description of applied codes

Physician giving information on...	the patient's disease personalised medicine the clinical trial possible side effects treatment and its procedure
Physician explaining the purpose of...	the clinical trial treatment
<i>Patient giving informed consent</i>	
Questions regarding the patient's...	well-being perception of his/her disease
Questions on whether something is clear/unclear to the patient	
Leading questions by the physician	
Physician asking the patient questions on treatment and its procedure	
Physician asking questions, which remained unanswered by the patient	
Physician's evaluation of patient's comprehension	
Physician's questions on the patient's information preferences	
Motivating the patient...	to be proactive to make autonomous decisions to participate in shared decision-making to participate in the clinical trial
<i>Physician's communication behaviour</i>	
Physician's evaluation of...	the clinical trial the disease the patient side effects treatment and its procedure
<i>Medical history</i>	
Patient's questions regarding...	the disease personalised medicine the clinical trial side effects treatment and its procedure
Patient's experiences...	with receiving information from physicians regarding medicine/medical treatment regarding the disease
<i>Patient's communication behaviour</i>	
Patient's private aspects	
Patient's evaluation of...	the disease giving informed consent making autonomous decisions regarding treatment personalised medicine shared decision-making the clinical trial side effects the treatment and its procedure
Patient's medical knowledge	
Disruptions of the consultation through...	third parties or a telephone call spatial conditions

3.2 | Genetic responsibility as genetic misconception

This form of responsibility entails the responsibility for relatives due to the assumption of genetic kinship. To date, it is a form of motivation for medical research participation or treatment mainly discussed

in the field of reproductive decision-making, childhood genetic testing and genetic risks in general (Arribas-Ayllon, Sarangi, & Clarke, 2008; Hallowell, Cooke, Crawford, Parker, & Lucasson, 2008; Schicktzan & Kogel, 2014). However, we also detected it in the context of personalised medicine. This seems to be triggered by the physicians' statements including wording such as "important for your children," "your children can benefit," "genetics of your tumour."

In the consultations, thus, wording involving "children," "consequences," and "genetics" could likely trigger genetic responsibility as these terms imply personal involvement and responsibility through parenthood. Potential benefit for children as such, however, actually is not an aim of the clinical trial on biomarkers. And genetics in this case does not necessarily entail heredity.

Dr. F.: But it also all depends on the genetics of your tumour. [...] The conception of the clinical trial thus far has no impact on your treatment. But it could potentially be essential for your children who both have chronic intestinal illnesses. It is important to note that within this clinical trial we are only examining the genetics of your tumour and not that of your person.

However, statements linked to presumed genetic responsibility did not occur in the ICFs. Also terms such as "family" or "relatives" could not be found in these documents.

Nevertheless, interview statements echoed the motivation uttered in the consultations. Some patients understood that the aim of clinical trial is to provide potential benefit for their own relatives or children in the future.

Ms. 13 B, 1st interview: [...] And possibly even for my children [...] That is also very important to me. [...] If something results from that so that they immediately are included in the screening program.

Mr. 25 A, 1st interview: [...] How the medication or the treatment has an effect [...] that's clear to me [...]. And I consented to it. [...] Because I have... two older kids [...] it doesn't have to help us anymore or it won't help us anymore [...]. And that's something [...] for our children and grandchildren.

Furthermore, the issue of misleading wording could particularly be seen in the detected motivation for genetic responsibility; we were astonished to learn that several patients believed that their research participation would likely help their own children, even in cases where no hereditary colon cancer was diagnosed. So we here identified a new form of "therapeutic misconception," context-specific for personalised cancer research. This genetic misconception indicates that wording such as "genetics" triggers strong, but false associations.

3.3 | Optimisation as personalised benefit

Personal interest and the hope for individual benefit were also commonly found as a form of motivation. Here, patients seemed to develop this

TABLE 3 Themes in the interview guidelines and exemplary questions (translated from German)

Understanding of disease, treatment and side effects	Which treatment was performed in the last few weeks regarding your rectal carcinoma treatment? How did you deal with the treatment physically and psychologically?
Attitudes towards and assessment of physician–patient communication; preferences for information	Do you remember the consultation with your physician? Could you tell me how the consultation took place considering further treatment which you consented to afterwards? What was especially important to you during the consultation? Do you remember if you wanted to know something specific? Was there anything that was not addressed during the consultation or that remained unclear? And if yes, was it resolved/clarified afterwards? Were there any situations or moments during the consultation and information on the part of the physician that you found difficult or problematic?
Experiences of the physician–patient relationship	How would you describe the ideal collaboration or relationship between a physician and a patient? Did you experience any critical moments during your current treatment? How did you personally perceive this consultation, maybe also in reference to other experiences you have had with consultations with physicians?
Motivation to take part in biomarker research	You consented to the so-called biomarker trial during this consultation. What do you expect from this participation?
Knowledge of, attitudes towards and assessment of future biomarkers/genetic tests	Can you tell me what is part of the clinical trial and what belongs to your standard treatment? Has your attitude or also opinion changed on prognostic tests regarding a physical response or also non-response to the cancer treatment after your current treatment? (Introduction to what the trial entails)
Knowledge of, attitudes towards and assessment of personalised medicine	What do you conceive of the term “personalised” or also “individualised” medicine? Can you conceive something of these terms? Do you see differences between both of these terms?

idea without being strongly prompted by utterances of the physicians. The patients' interests encompass how they are doing during their treatment, specific occurrences such as additional blood tests, hope for best treatment and the process of their treatment in general. Wording in the context of clinical trial participation such as “more intense supervision,” “advantage for you due to trial participation,” “treatment improvement,” “impact on treatment,” “study nurse” has an effect on the patients' understanding and motivation. It could affect patients' incomprehension regarding complex medical information and also trigger wishful thinking of receiving the best possible treatment and supervision.

The physicians' statements during the *consultations* may have led to the assumption of personal benefit in some form; triggered, for example, by more intense check-ups and contact with the study nurse, and also with the hospital personnel. Further, physicians referred to the great opportunity of being treated at this hospital specifically due to the clinical trial, although no benefit actually exists with the participation in the clinical trial on biomarkers. They emphasised that participation did not entail any disadvantages, which may trigger the assumption of personal benefit in an indirect manner.

Dr. AB: There still is something I'd like to talk about with you. You are very fortunate that you are being treated here. There is a large clinical trial running here at the moment. Have you heard of it?

Dr. V: [...] Later, our study nurse will come to see you. Nurse X., she can be seen as a further advantage for you.

In the ICFs, explicit and implicit wording can be found regarding the prospects of short-time benefits. Furthermore, detailed numbers are used to exemplify the possible benefit of the trial:

[...] We hope to increase the proportion of complete regression of the rectal carcinoma from 8% to 20% with this alteration of the treatment sequence. (ICF 2, p. 3)

In ICF 1 and 2 the possible benefits for the patients are directly addressed:

[...] It is possible that in 1 to 2 years we will gain new medical insights that will benefit colon cancer patients like you and maybe even yourself. (ICF 1, p. 4)

With the treatment within this clinical trial your chances of recovery could possibly be improved. (ICF 2, p. 7)

In the *interviews*, patients seemed to understand that with the research participation, check-ups, especially concerning blood levels, will be more regular. They interpreted this as personal benefit in the form of more intense supervision and optimised treatment in general. Further, some patients thought of participation being beneficial as it is something novel; others believed in a preventative effect meaning that it could help in the case of tumour recurrence. As the statements show, especially the wording in the consultations had an effect on the patients' conceptions. Also, increased test validity seemed to be a strong argument for the patients' benefit.

Ms. 9 B, 3rd interview: I know that a bit more blood is taken from me [...]. And they test a bit more intensely I think. [...] And they check the tumour and also take a sample of it. And then they check again, I mean properly.

It is important to note that more than one factor often contributed to the forms of motivation mentioned, combined forms of motivation were

not relevant in this context for exemplifying the most driving elements of motivation for clinical trial participation.

3.4 | Patients' incomprehension of stratification as the research aim

Above, we illustrated three common patterns of motivation related to the research aim. But the fundamental issue remains that the patients did not at all understand the actual aim of the clinical trial, namely future stratification according to response to (neo)adjuvant treatment. The terms "individualised" or "personalised" could rarely be detected in the material and the term "stratification" was neither used in the consultations nor in the ICFs although it is the defined aim of the clinical research group on biomarkers (Liersch, Rothe, Ghadimi, & Becker, 2009). Thus, it was also not mentioned by the patients later in the interviews. In some consultations the terms "responders and non-responders" and "tailored treatment" were used. However, also these patients still had difficulties in reproducing the actual aim of the clinical trial. Only very few comprehended the actual aim. Here, information paternalism seems to be a pattern, as physicians individually decided which and how much information was given.

As non-treatment is not an option for most patients (Wöhlke, Perry, & Schicktanz, 2015) it is problematic that patients did not understand the idea of the future scenario of stratification into responders and non-responders, the latter possibly resulting in non-treatment.

In most of the consultations, due to little time and the vast amount of information, physicians often summarised the objectives of the clinical trial in few sentences. If stratification was addressed in the form of response or non-response, the wording misled patients to a positive interpretation of stratification, because the "optimisation" of treatment was stressed. That some patients might not receive (neo)adjuvant treatment if the tumour were not to respond was not mentioned, even in this restricted setting where stratification only affects (neo)adjuvant radiation and chemotherapy treatment and not the whole treatment including an operation and palliative care. The use of abstract terms such as "genetics," "prognosis estimate," and "tumour biology" was confusing for patients and may have added to the over-burdening of some patients as the example of one patient shows below.

Dr. AB: [...] I have already told you that we examined in the clinical trial that it would be better to treat the tumour in advance. The results that have thus far been acquired in this clinical trial are very good already so that we now want to try to optimise the treatment by trying to tailor the treatment for the individual patient. So that, in the future, one could see on the basis of markers if more radiation can be given.

Dr. F.: But it also all depends of the genetics of your tumour. [...] They are looking for key changes of proteins and mitogens that could be responsible for response or non-response of the tumour to treatment. Of course we are not yet advanced enough to make assertions about

your tumour and to which group your tumour belongs. The concept of the clinical trial [...] does not have any impact on your treatment thus far.

Mr. 21 A, 2nd interview: [...] because I can't make sense of some of the terms other people have to explain them to me. When the doctor explains it to me, he explains it so quickly that I immediately forget it again.

As mentioned above, the term "clinical trial" was used very heterogeneously within the ICFs. At the beginning of the form it was mentioned that patients are treated within the clinical trial. The word stratification, however, did not occur in the forms.

The treatment of the carcinoma takes place within the clinical trial. (ICF 1, p. 2; ICF 2, p. 3)

Later on, the term "clinical trial" was used in combination with the term "scores" which might help to better predict response in the future, the technical language may have inhibited patients from understanding the description of the clinical trial. Further, the aim of the clinical trial was described as to better predict response by new lab methods and blood tests. Thus, the overlap of information about what consequences the clinical trial has for the actual treatment of the patient and what is just a future aim was indistinguishable.

So-called KFO-scores were developed with which the response to treatment, treatment effect and the further course of illness can probably be better predicted. Now we want to verify how good the scores are. Within the [clinical trial] we want to verify with 200 further patients in different hospitals of a research network if the previously gained insights will endure. (ICF 1, p. 3; ICF 3, p. 1)

The aim of our research is to test and develop new laboratory methods in order to better predict response of rectal carcinomas to treatment on the basis of your blood and samples and specimens. (ICF 1, p. 3) In this context, molecular biology and genome-wide studies are planned to investigate the characteristics of the tumour and normal tissue more precisely. (ICF 3, p. 3)

In the interviews many patients claimed not to remember at all what the clinical trial entailed. Still, the majority of patients named additional blood samples which they could often not differentiate from those samples taken in the context of treatment. Especially in the second and third interviews, this was all they remembered. If patients did remember more detailed aspects, they mainly focused on "optimised" and "tailored treatment." Some patients named the establishment of a genetic database as an aim of the clinical trial, often linked to the above-mentioned solidarity as a form of motivation.

Only very few patients understood the complex aims of the clinical trial. However, it is important to note that those patients, who

understood the concept of stratification and supported it, did this against the background that they responded positively to treatment.

Mr. 18 B, 1st interview: Personalised medicine? [...] Not just that any kind of concepts are developed for the masses but that it is individually adopted to the individual patient [...]. And that one refers to the individual person [...] and not just to the masses as it might have been done in the past. That you say with a cold you will get this and that medication [...].

One patient stressed the negative implications of being stratified as a non-responder, and feared the consequence of being treated as a second-class patient. This also indicates that non-treatment in terms of not receiving (neo)adjuvant treatment in the context of stratification does not seem to be an option for patients.

Mr. 26 A, 1st interview: If I were then told that here no treatment would respond, then you'd have gotten the shit end of the stick which wouldn't be that great concerning test validity. Then you'd be a B-class patient. Along the lines of, well you, we won't treat at all.

Our findings overall illustrate that in the conveyance of stratification in the clinical context this fundamental issue remains insufficiently addressed in the consultations and in the ICFs.

4 | DISCUSSION

Our results provide insight into how cancer patients involved in personalised cancer research assess and (mis)interpret the information provided or are misled by wording used by the physicians. A reason for the latter might be that doctors are entangled in a conflicting role while not only acting as physicians but also as researchers pursuing certain research interests, wording can, as a result, be implicitly biased. It must be emphasised that our empirical-ethical study is based on a restricted sample of colorectal cancer patients in one hospital. However, to our knowledge, it is the first longitudinal analysis of patients' views focusing on potential misconception related to personalised medicine. The research setting allowed an in-depth analysis of patients' understanding and recapitulated knowledge during research participation. Notably, the understanding mainly refers to the information provided orally by the physicians. Written ICFs were much less important. This was perhaps also due to the fact that patients seldom fully read the ICFs during the consultations, as far as we could observe, and rarely followed up on reading at home, even when encouraged to do so by the physicians.

Considering patients' patterns of moral motivation for research participation, considerable influence of the physicians with their communication and wording must be assumed. While solidarity is found to be the strongest pattern of motivation, genetic misconception and personal benefit also played an essential role. A closer look revealed

that statements of solidarity and genetic misconception were evoked by the manner in which researchers and clinicians framed the moral context. As highlighted in the results, very few statements were found supporting altruism; the concept of altruism, in our opinion, needs to be clearly separated from the concept of solidarity (Newington & Metcalfe, 2014; Osteen, 2002) because altruism rather refers to true commitment and taking on risks although clearly knowing that one will not directly profit from this research. Other studies (Godskesen et al., 2013; Truong et al., 2011) suggested "altruism" instead, but provided pre-formulated answer options in a survey or did not control for the input provided by the physicians as we did. Calls for solidarity in the biomedical context are currently reinforced very theoretically (Prainsack & Buyx, 2011) to increase citizens' and patients' willingness to participate in research and share genetic data or tissue. Our study points to the empirical importance of solidarity, as well. However, given the detected risk of patients' adherence to physicians' expectations as already described by Townsley et al. (2006), we fear that using rhetoric of solidarity can lead to socially desirable behaviour of patients but undermines their intrinsic motivation or even may create mistrust in some cases.

Furthermore, the effect of misleading wording becomes particularly apparent in the findings of patients' genetic misconception (McKibbin et al., 2014; Pentz et al., 2012). This phenomenon is likely to be essential for any molecular cancer research when physicians refer to genetics, gene banks, genetic testing or tumour genetics (Beskow, Dombeck, Thompson, Watson-Ormond, & Weinfurt, 2015; Gray et al., 2012). Not mentioning "genetics" is not what we suggest, but it should be embedded in a more detailed description of what is heritable and what is not. In several cases, "genetics" might be replaced by more general molecular biological explanations.

The lack of understanding of stratification by patients can be seen as a particular ethical problem rooted in a modern, cultural context of dealing with cancer. With the general notion that stratification is an important improvement to reduce unnecessary side effects for non-responders, new forms of transparent communication are needed to gain public acceptance of tailored treatment. General wording such as "optimisation" or "personalisation" tend to undermine (rather than facilitate) the correct understanding of this important research aim. The common habit of drawing on optimistic communication strategies for bad or also precarious information on treatment conflicts with the clear communication of the concept of non-response within stratification or as a consequence of early palliative treatment. Patients tend to collaborate with physicians in optimistic conveyance strategies (Leydon, 2008) or deny the seriousness of their illness especially in the beginning of treatment (Vos & de Haes, 2007). Further, many patients conceive of cancer treatment as entailing an active process of removing, cutting or radiating.

The acceptance of non-treatment is generally very low among patients in the case of cancer and is especially not seen as an option for elderly patients (Elkin, Kim, Casper, Kissane, & Schrag, 2007; Solomon et al., 2003). The low acceptance among patients may also exist among physicians, except for when palliative care is offered at

a very early stage (Miller, 2014). In our sample, palliative care was rarely addressed during the physician–patient consultation and also not mentioned by patients during the interviews, even in very difficult cases. Therefore, we assume that there was a low awareness of such an alternative form of treatment. Interestingly, Temel et al. (2010) found that early communication of palliative care leads to significant improvement in patients' well-being even when palliative care was not necessary in the end. This is another indicator that communication might have strong psycho-somatic impacts and also is important for patients' autonomy.

As our results indicate, denial is only one possible explanation of why the patients did not comprehend the aim of stratification. Stratified treatment, which conceptually involves non-treatment, here, in terms of (neo)adjuvant treatment as a standard option, poses an immense cognitive and moral challenge to patients. Because many patients hold on to the established treatment, active treatment seems a necessity. In this sense, patients are not in denial but take on a moral position expecting medicine to always provide treatment. This observation is in line with the practice of offering palliative oncology care as treatment and not as sheer non-treatment or withdrawal. As this information is not easily absorbed by patients, consultations should be intensified and should be empathic about the option of non-treatment (Halpern, 2014; Halpern & Arnold, 2008; Swindell, McGuire, & Halpern, 2010) or in cases where stratification is not equivalent with non-treatment per se, patients, when fully informed, could also be more accepting of alternative treatment options. Given the detected low impact of written information, such as ICFs, the role of documents should critically be assessed also by ethicists and lawyers. Despite the high level of formal safeguarding of written consent forms through ethics committees, the actual practical consultations are not sufficiently examined or reflected on. This constitutes an ethical problem in the context of IC in clinical trial participation. However, if the content of the ICFs also does not give patients the possibility of comprehensibly informing themselves, these must be altered and possibly combined with alternative strategies.

4.1 | Future directions

Our findings will hopefully help with shaping and sharpening the opaque but also important paradigm of 21st century personalised medicine by providing a more personalised communication practice between physicians and patients. We advocate for the development and testing of alternative measures of preparing and conducting IC consultations. Only an approach that is sensitive to possible misunderstandings and wording impacts can be justified as nudging (Aggarwal et al., 2014). Audio-visual approaches have shown to act as a supporting measure for understanding complex medical information distributed to patients before the first consultation (Synnot, Ryan, Pricor, Fetherstonhaugh, & Parker, 2014). However, as other studies have shown, additional material has its limitations (Flory & Emanuel, 2004) and must also be further developed. The role of physicians is crucial for patients regarding the potential of both understanding and

misunderstanding. Hence, physicians need more training, support, and recognition for this aspect of their responsibility to improve patients' understanding.

It is important to note that our aim was never to devalue the treating physicians' abilities but rather to pinpoint crucial issues in physician–patient communication with regard to IC and understanding of clinical trial participation. Further research in other local settings, such as cross-cultural comparisons, is needed to test our hypothesis that this is a ubiquitous phenomenon related to personalised medicine. Thus, we do not recommend reducing personalised medicine to 'biomedical stratification,' but rather call for a stronger use of the paradigm change in the sense of a "person"-alised-centred perspective. Future communication tools should be directed from a model in which the patient is seen purely as a passive target of a medical intervention to another model where a more contractual and deliberative arrangement is made by actively involving the patient (Sandmann, Granger, Ekman, & Munthe, 2012).

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CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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