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Ethics of Genetically Determined Chronic Diseases – Hereditary Chronic Pancreatitis as an Example

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CONTENT

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LIST OF ABBREVIATIONS

HCP	Hereditary Chronic Pancreatitis
HP	Hereditary Pancreatitis
PAO	Patient Advocacy Organization
QCA	Qualitative Content Analysis

LIST OF PUBLICATIONS

Article 1

Mueller R, Aghdassi AA, Kruse J, Lerch MM, Rach C, Simon P, Salloch S. Lived experience of hereditary chronic pancreatitis - a qualitative interview study. Chronic Illn. 2021 Sep 24:17423953211039774. doi: 10.1177/17423953211039774.

Article 2

Mueller R, Aghdassi AA, Kruse J, Lerch MM, Simon P, Salloch S: Perceptions of genetic testing in patients with hereditary chronic pancreatitis and their families: a qualitative triangulation. Eur J Hum Genet 29, 29–38 (2021). https://doi.org/10.1038/s41431-020-00705-9.

Article 3

Mueller R, Rach C, Salloch S: Collective forward-looking responsibility of patient advocacy organizations: conceptual and ethical analysis. BMC Med Ethics 22, 113 (2021). https://doi.org/10.1186/s12910-021-00680-wArticle 4.

Article 4

Rach C, Lukas J, Mueller R, Sendler M, Simon P, Salloch S: Involving patient groups in drug research: a systematic review of reasons. Patient Prefer Adherence. 2020;14:587-597. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7075437/.

INTRODUCTION

Hereditary Chronic Pancreatitis

Hereditary chronic pancreatitis (HCP) is a rare genetic disorder of the pancreas. Complex interactions of genes and environmental factors affect the development and course of the disease. The hereditary variant of pancreatitis (HP) typically starts with acute pancreatitis in childhood and develops via recurrent acute to chronic pancreatitis in the second or third decade of life (Weiss et al. 2019). However, the traditional classification in acute (sudden onset; duration less than 6 months), recurrent acute (more than one episode of acute pancreatitis) and chronic pancreatitis (duration over 6 months) (Shelton et al. 2020) as different disease entities has been widely replaced by the idea of a disease continuum because of common etiological and genetic risk factors and a significant overlap in the clinical manifestations and phenotypes (Weiss et al. 2019). Although there are different origins and risk factors for pancreatitis, such as gene mutations, alcohol or autoimmune causes, all variations manifest similar clinical symptoms (Raphael et al. 2016). However, gene mutations are a rare cause and lead to special characteristics of HP, for example, its earlier median age of onset of 10 years (Weiss et al. 2019). Further, specific features of HP are an increased risk of exocrine insufficiency, diabetes and pancreatic cancer (Raphael and Willingham 2016). In general, patients with HP do not have increased mortality compared to the general population (Rebours et al. 2009), but an increased risk of developing pancreatic cancer (Rebours et al. 2012, Raphael and Willingham 2016). Although HP is defined as a rare disease, the exact prevalence and incidence are unknown. The estimated prevalence of HP ranges from 0.125 to 0.57 per 100,000 people in different European countries (Rebours et al. 2012, Raphael and Willingham 2016). But because of many wrong or undiagnosed cases, the exact numbers are probably higher, and regarding the worldwide prevalence, there is no reliable data at all.

In its chronic form, the continuing inflammation of the pancreas comes with degeneration of the exocrine and endocrine pancreatic tissue and irreversible morphological changes (Weiss 2019). The more recurrences, the more changes develop, which finally evolve into damage of the pancreas: from fibrosis (Apte et al. 2011), parenchymal calcification, pseudocysts (Lerch et al. 2009), bile duct and duodenal obstruction (Menges et al. 2000) to endocrine and exocrine pancreatic insufficiency (Raphael and Willingham 2016, Aslam et al. 2021). Due to

the endocrine insufficiency, diabetes mellitus is often developed; as a result of the exocrine insufficiency maldigestion, steatorrhea and weight loss can occur (Weiss et al. 2019). Acute phases of HP include abdominal pain, nausea, vomiting and diarrhea. The course of HP varies regarding onset, progression over time, frequency and intensity of the acute pancreatitis attacks. Due to the recurring symptoms, especially the pain and the accompanying medical interventions and hospitalizations, HCP is associated with a reduced quality of life (Cronin et al. 2013, Boije et al. 2019).

Very often, HCP is mis- or undiagnosed and, at least at the moment, no effective interventions for treatment or prevention exist. The therapy focuses on preventive measures (e.g., avoiding triggers such as tobacco, alcohol, stress and dietary modifications [Wiese et al. 2021]), medical management (e.g., exogenous pancreatic enzyme replacement or pain control), treatment for endocrine and exocrine insufficiency, endoscopic therapy (e.g., decompression of obstructed pancreatic ducts [Dumonceau et al. 2019]) and surgical treatment for the management of pancreatic necrosis or drainage of pancreatic cysts up to partial or total pancreatectomy (Raphael and Willingham 2016). The course of HCP, acute episodes, pancreatic insufficiency and the occurrence of pancreatic cancer are unpredictable (Teich et al. 2008). HCP management covers treatment of the symptoms, especially the pain, regular screenings of pancreatic exocrine and endocrine insufficiencies and screening for early pancreatic cancer. In addition, supportive care, such as social workers, psychologists or patient groups, can be helpful in the management of the disease (Rebours et al. 2012).

Pancreatitis as a genetically determined condition was first described by Comfort and Steinberg in 1952. In 1996, the first genetic defect leading to HP was identified (Whitcomb et al. 1996). Since then, multiple genetic mutations on several genes, for example on the cationic trypsinogen gene (PRSS1) (Nemeth et al. 2014), have been identified as relevant etiologic factors for developing HP (Weiss et al. 2018, Suzuki et al. 2021, Wertheim-Tysarowska et al. 2021). The Chronic Pancreatitis Genetics Risk Factors Database covers a comprehensive list of genetic mutations associated with HP (Sahin-Toth et al. 2021). The numerous mutations have a different but usually high penetrance (Raphael and Willingham 2016). Studies reported, for example, an estimated penetrance of about 77-93% for patients with PRSS1 gene mutations (Rebours et al. 2012). HP is transmitted in both autosomal recessive and autosomal dominant fashion, but the more common inheritance pattern is autosomal dominant (Raphael and

Willingham 2016). In any case, the inheritance pattern is complex: in addition to a genetic mutation or a combination of genetic mutations, environmental factors also play a part (Raphael and Willingham 2016). Although multiple genetic mutations, which are associated with the development of HP, can be identified with genetic screening today, the genetic information has, at least at the moment, no therapeutic implications (Suzuki et al. 2021, Wertheim-Tysarowska et al. 2021).

Despite the immense research at the molecular and clinical level and the increased knowledge about HCP, social and ethical aspects in the context of HCP have not been investigated systematically, yet. A few qualitative studies examined the impact of chronic and acute pancreatitis on health-related quality of life, daily activities and social life (Cronin and Begley 2013, Boije et al. 2019, Shelton et al. 2020). A phenomenological study, for example, described the patients' perceptions of recovering from acute pancreatitis attacks and emphasized the physical and emotional burdens during these attacks (Boije et al. 2019). But not only the acute version, also the chronic form of pancreatitis is associated with psychological burdens for the patients affected (Johnson et al. 2019). A qualitative study with patients with chronic pancreatitis highlighted the permanent experience of suffering at the physiological and psychological level (Cronin and Begley 2013). Furthermore, the emotional and psychological burdens, such as uncertainties and worries, affect not only the patients but also their relatives (Shelton et al. 2020). Family members described, for example, the experience of seeing relatives affected by pancreatitis as a disturbing experience (Applebaum-Shapiro et al. 2001). Although there is some qualitative research on acute and chronic pancreatitis, there has been far less qualitative research on patients' experience with the rare hereditary variant of the disease. However, the fact that the disease is rare, hereditary and chronic may lead to a unique illness experience and specific ethical and social challenges for patients and their families. The existing research on acute and chronic pancreatitis and, accordingly, the therapy options and support available may thus not be directly transferable to HCP. Instead, the existing research needs to be expanded to obtain a comprehensive picture of what needs to be done when caring for patients with HCP and their relatives.

Research Questions and Aim of the Thesis

The interplay of the three dimensions of *rarity, inheritance* and *chronicity* can result in a unique experience of HCP and specific ethical and social challenges for the affected patients and their families. The aim of the current thesis is to investigate, firstly, the individual experience of HCP and, secondly, the ethical and social aspects in the context of the disease to better understand HCP and its implications for those affected (Table 1).

The lived experience of patients with HCP and their relatives is taken as a starting point. The aim is to acquire a first-hand understanding of living with HCP, focusing on the chronic character of the disease. The main research question of this experienced-based part of the thesis is 'How do HCP patients and their families experience their lives with a rare, genetically determined, and chronic-recurrent disease?'

Because the specific experience with the hereditary variant of the disease has been less researched so far, a subsequent question focuses on the experience of the patients and their relatives with issues originated through the hereditary dimension of the disease. Since genetic issues, such as genetic testing, lead to complex challenges not only for the individual patients but also for their families, the question of the second part of this thesis is 'What are the ethical and social issues experienced by patients and their families regarding genetic testing for rare chronic diseases such as HCP?'

Based on the empirical findings, the ethical and social aspects in the context of HCP are analysed. Since the rarity of HCP leads to difficulties for patients and their relatives in finding immediate and appropriate help, patient advocacy organizations (PAOs) might be relevant agents in this context as they represent further sources for support. However, it is not clear, in what sense and to what extent PAOs can be understood as responsible for the patients. The focus of the analytical part of this thesis is, therefore, on the specific responsibility of PAOs. The third research question 'What is the moral responsibility of a patient advocacy organization?' is addressed and PAOs' responsibility systematically analysed.

In the current thesis, HCP is taken as an example to elucidate the social and ethical issues in the context of a rare, genetically determined, chronic disease. As the first qualitative study with HCP patients and their relatives, the present thesis illuminates the experience of this

specific group and, at the same time, expands previous research on the ethics of genetically determined chronic diseases.

Table 1: Study parts of the thesis.

PART	AIM	QUESTION	METHOD	PUBLICATION
EMPIRICAL PART	Collecting first-hand experience of those affected by HCP to better understand the disease and living with it.	How do HCP patients and their families experience their lives with a rare, genetically determined, and chronically-recurrent disease?	Qualitative individual semi-structured interviews; QCA; Ethical Analysis	**Mueller** et al. Lived experience of hereditary chronic pancreatitis – A qualitative interview study and ethical analysis (2021a)
	Identification of ethical issues regarding genetic testing in family contexts.	What are the ethical and social issues experienced by patients and their families regarding genetic testing for rare, chronic diseases such as HCP?	Focus group; QCA; Ethical Analysis	**Mueller** et al. Perceptions of genetic testing in patients with hereditary chronic pancreatitis and their families: a qualitative triangulation. Eur J Hum Genet (2021b)
ANALYTICAL PART	Understanding the responsibility of patient organizations in the context of hereditary, chronic diseases using the example of participation in research.	What is the moral responsibility of a patient advocacy organization?	Ethical and Conceptual Analysis; Systematic Review of Reasons; QCA	**Mueller** et al. Collective forward-looking responsibility of patient advocacy organizations. Conceptual and ethical analysis (2021c)
				Rach C, Lukas J, **Mueller** et al. Involving patient groups in drug research: a systematic review of reasons (2020)

QCA: Qualitative Content Analysis.

THEORETICAL BACKGROUND

Subjective Experience and Ethics of Chronic Diseases

Although the term *chronic disease* is commonly used in health policy, research and academic literature, there is no clear definition of it (Bernell et al. 2016). The World Health Organization defines chronic conditions as those which 'tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioural factors' (WHO 2018). As in many other definitions (Department of Health and Social Care 2012, The King's Fund 2018, NHS 2018), the emphasis is on the long-term dimension. However, this simplification does not meet the complexity and wide variety of chronic conditions, ranging from non-communicable to mental and infectious diseases. It is not the aim of this section to engage in the discussion on the conceptualization of chronic diseases, but to acknowledge the ambiguity of the term and to take an open perspective for the further reflections.

The lived experience of chronic illness has received increasing research interest in the medical and sociological literature since the 1980s (Strauss et al. 1984, Kleinman 1988, Bury 1991, Frank 1997, Lawton 2003, Carel 2016, Synnes et al. 2020). The subjective perceptions of the patients have become a relevant part of chronic illness research, especially through two perspectives: first-person experience of chronic diseases (Toombs 1993) and qualitative research with patients with chronic conditions (Bury 1982). The start of the debate was dominated by rather negatively connoted concepts, such as suffering and disruption (Bury 1982), but there was a shift in the 1990s to more positive topics, such as hope and empowerment (Sally et al. 1998). Today, individual coping strategies (Delmar et al. 2005, Ferguson et al. 2014), self-management (Newbould et al. 2006) and the consequences of a chronic condition for the identity of patients, especially of young patients (Venning et al. 2008, Bray et al. 2014, Maslow et al. 2016), for work (Edwards et al. 2007), social (McQuoid 2017) and family life (Gregory 2005, Rosland et al. 2012) and practical and moral dilemmas in living with a chronic condition (Townsend et al. 2006) are strongly discussed themes in the context of chronic illness research.

Since the beginning of the debate, the concept of biographical disruption according to Bury (1982) has often been used as a theoretical background for research projects on the experience of chronic conditions. Bury (1982) conceptualized chronic illness as a disruptive

experience and the onset of a chronic illness as a biographical disruption, distinguishing a life before and after illness onset and forcing the patients to rebuild their biography. The more recent literature emphasizes the limitations of Bury's concept and claims for more differentiated conceptions, such as normal illness (Williams 2000), biographical reinforcement (Carricaburu et al. 1995), biographical flow (Faircloth et al. 2004), recurrent biographical disruption (Saunders 2017) or biographical contingency (Monaghan et al. 2015). Some of these approaches share the understanding of living with a chronic condition as a predictable linear path. In Paterson's view (2001), however, the idea that patients with chronic conditions follow a trajectory is misguiding. Her 'shifting perspectives model' of chronic illness describes, instead, living with a chronic condition as an ongoing, continually changing process: either elements of illness (i.e. illness dominates the daily life) or wellness (i.e. illness is largely unnoticed) can be in the foreground (Paterson 2001). Due to strong variations in the clinical course of HCP known from the literature, Paterson's model seems to be a suitable lens for the current study because the model allows variation and individualization of the illness experience.

Ethical issues regarding chronic conditions have received little systematic reflection in bioethical literature for a long time (Jennings et al. 1988, Gibson et al. 2012). Today, however, there are broad bioethical debates on the patients' autonomy and the physician-patient relationship (Moros et al. 1991), especially regarding (non-)adherence (Walker 2019, Stutzin Donoso 2020), discrimination and stigma (Brown 2015), the challenges for policy and healthcare systems (Mayes et al. 2013, Klingler et al. 2015), the situation of healthcare professionals (Gaille 2018), caregivers and family members (Gregory 2005, Rosland et al. 2012) and questions of epistemic (Byrne 2020) and social (in)justice (Casswell 2016). Walker, for example, gives a comprehensive overview of many ethical issues that arise in the specific context of chronic conditions (Walker 2019). Some authors within the bioethical debates surrounding chronic conditions claim for ethical frameworks dealing with chronic conditions, which are expected to be patient-centred and consider the lived experience of those who are affected by chronic conditions (Jennings et al. 1988, Gibson and Upshur 2012, Edwards et al. 2014, MacKenzie et al. 2015). As the awareness of the needs and values of those affected can enrich the ethical analysis and eventually help to deliver appropriate care to patients with chronic conditions (Wagner et al. 2001, Epping-Jordan et al. 2004, Desmedt et al. 2018), the ethical analysis in the current thesis is based on the empirical findings.

Ethics of Genetic Testing in Family Contexts

For many chronic conditions, genetic testing is available today. Genetic testing generally refers to the analysis of DNA to detect changes in gene sequence or expression levels (AMA 2021). It can also include 'the analysis of RNA to determine gene expression, biochemical tests for the presence of gene products and for microscopic analysis of chromosomes' (AMA 2021). The most relevant types of genetic testing for chronic conditions are diagnostic and preventive genetic testing. Diagnostic genetic testing can identify whether a symptomatic individual has a certain genetic disease (AMA 2021). Predictive or presymptomatic genetic testing can determine whether an individual has an increased risk of developing a particular disease or identify a genetic disease that will manifest later in life (AMA 2021).

An early diagnosis through genetic testing gives the patient an explanation about the origin of their disease. This knowledge can be relevant for coping with the disease, especially when the correct diagnosis would otherwise take a long time, which is often the case in rare diseases (Global Genes 2021). An unknown diagnosis can be of significant psychological distress for the individual patients and their families, causing difficulties for healthcare professionals and an economic burden to healthcare systems. For an optimal management of rare chronic diseases like HCP, a precise and early diagnosis is significant. Furthermore, genetic testing can provide useful prognostic information and options for family planning. The presymptomatic testing can identify carriers and asymptomatic individuals and, thus, contribute to potential prevention.

However, the impact of genetic information depends on various factors, such as the person affected, the condition being tested and the social context of the test (Parens et al. 2019). The test results can lead to unintended adverse reactions, emotionally but also behaviourally (Heshka et al. 2008, Dar-Nimrod et al. 2014), especially when the testing is conducted without a professional counsellor or medical intermediary. There is an intensive debate on the management of genetic testing and corresponding information, not only in medical research but also from sociological (Wade 2019), psychological (Crozier et al. 2015, Roberts 2019) and ethical perspectives (Nyrhinen et al. 2004, Brierley et al. 2012, Soden et al. 2012, Roberts et al. 2013, Clarke 2014). Issues such as patient autonomy and informed consent (Soden et al. 2012), the counselling process (Clarke et al. 2019), complexities and consequences of genetic

information (Soden et al. 2012, Clarke 2014), incidental findings (Davey 2014), discrimination and stigmatisation (Manz 2016) are strongly discussed.

As genetic information does not only affect the tested person but also their family, the bioethical debate on genetic testing also entails family issues. Topics in the discussion include family planning and reproductive decision making (Decruyenaere et al. 2007), prenatal testing (Biesecker 2019, Grob 2019, Werner-Lin et al. 2019), sharing genetic information within families (Forrest et al. 2002, Forrest et al. 2008) and the impact of this information on family members (Gilbar et al. 2012). Decisions regarding healthcare have been analysed in the bioethical literature for a long time from the perspective of the individual person. Many authors, however, have distanced themselves from this individualistic perspective and claim a new way of thinking about the relationship of families and healthcare (Verkerk et al 2015, Verkerk et al 2019, Kihlbom et al 2019). As an 'ethics of families' understands families as intrinsic and inseparable from certain health-related ethical choices, such as decision-making in the context of genetic testing (Cowley 2019), it seems to be an adequate lens for the current study.

Moral Responsibility of Patient Organizations

Similar tendencies, away from individualistic towards relational or collective perspectives, can also be noted in other bioethical debates. A 'relational turn in bioethics' (Jennings 2016) has been marked by Jennings some years back, and in many bioethical discussions, for example in debates about patient and public involvement (Hainz et al. 2016), the focus on the individual is no longer sufficient. Particularly in the context of rare and chronic diseases, such as HCP, self-help groups, patient associations and health movements are important sources of support for patients and their families (Epstein 2008, Edwards 2013). Although these groups are very heterogeneous, they share the idea that individuals together have better opportunities to help each other and more power to advocate for their interests (Epstein 2008).

Especially, PAOs are gaining an increasingly important role in health policy, healthcare systems and biomedical research (Rabeharisoa 2008, Wehling et al. 2015). Their strong increase in the last few decades can be ascribed to the patients themselves, who campaign for patient rights and participation, and to political recommendations for more patient involvement in decisions

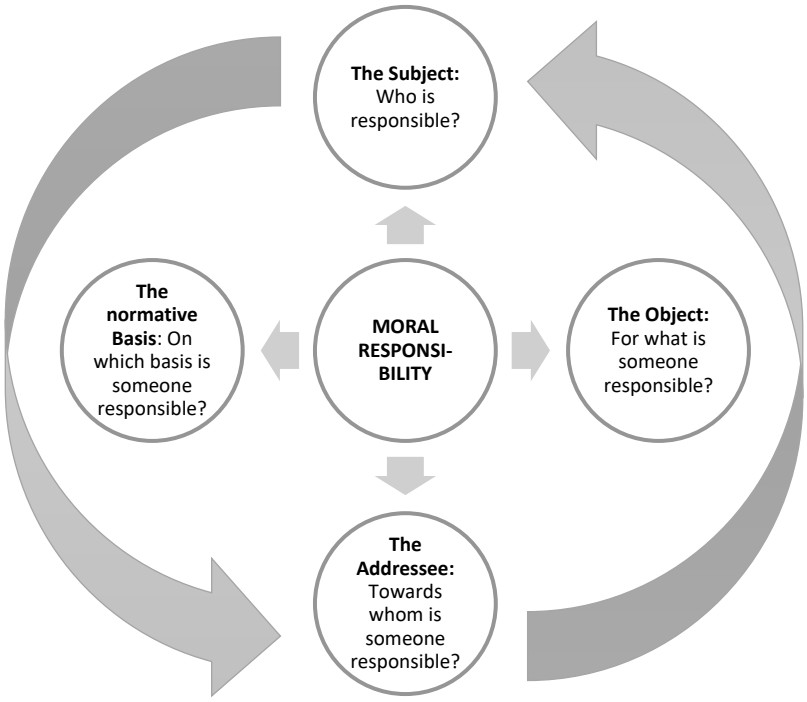
about health issues (WHO 1994, Enquete-Kommission 'Zukunft des Bürgerschaftlichen Engagements' des Deutschen Bundestages 2002, Department of Health and Social Care 2010). The organizations vary greatly in terms of size, professionalization, finances and geographic scope, ranging from small local groups to national, international and global organizations (Epstein 2008). They cover a broad range of health issues, goals and activities, such as advocating for those affected, lobbying for (or against) certain research fields, changing medical practice, influencing health policy and opposing stigmatization, discrimination and exclusion (Epstein 2008). Despite their diversity, typical attributes for PAOs are their non-governmental, non-profit and patient-driven character (European Medicines Agency 2018). The common goal is to strengthen the voice of affected, and sometimes overlooked individuals, and ensure that their needs are acknowledged (Sienkiewicz et al. 2017). However, PAOs represent different interests at the same time: the interests of their members, typically patients and their relatives, caregivers and non-members suffering from the same problem. In addition, they often work together with healthcare professionals and scientific, political and industrial stakeholders.

Despite their affirmative goals, the legitimacy of the PAOs' activities is intensively discussed in bioethical literature. Among the controversial issues are, for example, the construction of knowledge (Schicktanz 2015), the problem of representation (Jongsma et al. 2018), the involvement of patients in politics (Baggott et al. 2018) and research (Rabeharisoa et al. 2002) and the cooperation with industrial stakeholders (McCoy et al. 2017, Rose et al. 2017, Ehrlich et al. 2019). This wide-ranging discussion shows that PAOs are confronted with various ethical issues. For example, within the possible involvement in research, PAOs are faced with ethical questions regarding informing and engaging their members to participate in said research. Confronted with decisions of ethical significance, PAOs have to build their own positions and justify their decisions. The required justification of their decisions and actions indicates that PAOs' activities have a moral character, are subject to ethical evaluations and are linked with the normative concept of responsibility. However, it is not clear what moral responsibility means for a group like a PAO.

The concept of moral responsibility has gone through long and complex debates in philosophy (Talbert 2019), (bio)ethics (Schicktanz et al. 2012), medicine and healthcare (Agich 1982), for example, concerning the individual patient's health-related behaviour (Brown 2013, Langanke

et al. 2015) or collective responsibility in healthcare (Downie 1982, French 1982). Despite these diverse debates, responsibility can generally be differentiated in a causal and a normative relation (Langanke et al. 2015). Causal responsibility means that someone or something has caused something, like a storm has caused damage to a roof. In this example, the attribution of the consequences remains a descriptive ascription. Responsibility in normative terms demands more; it demands that the agent, who caused something, justifies their action and the following consequences (Langanke et al. 2015). Which specific conditions the agent must fulfil to be ascribed responsibility, for example, free will, remains controversial, but there is agreement in literature that at least some epistemic conditions and some conditions of control have to be fulfilled. In the context of PAOs, the meaning of responsibility as a normative relationship is of interest. As such, responsibility manifests in relations between different reference points (relata). Although there are concepts using up to six (Langanke et al. 2015) or seven (Schicktanz and Schweda 2012) reference points, the following four relata seem at least necessary for moral responsibility: someone (the subject) is responsible to somebody (the addressee) for something (the object) regarding normative criteria (Figure 1). As the relational understanding of responsibility is a useful analytical tool to analyse activities of PAOs that are characterised by questions of responsibility, it seems to be a suitable approach for the following analysis.

Figure 1: Moral responsibility as a relational concept with four reference points.



METHODS

The current thesis includes different sections using several methodologies: starting with a qualitative empirical study, combined with ethical and conceptual analysis, and followed by a systematic review of reasons (Table 1).

Qualitative Empirical Research Design

Although often criticized, the dichotomy of quantitative and qualitative research methods is, especially in the social sciences, omnipresent: 'On the one hand stands a rigid positivistic conception of research with a quantitative, experimental methodology, on the other hand an open, explorative, descriptive, interpretive conception using qualitative methods' (Mayring 2014). The selection of the method depends, among others, on the object and goal of the research. For example, to collect subjective experience or investigate previously unknown (social) phenomena, qualitative methods are needed. By contrast, to confirm previously defined hypotheses, explain causal relationships and generalize numerable statements, quantitative methods are appropriate. In the current thesis, the missing research on the subjective experience of patients with HCP and their families influenced the study aim, the research questions and finally the chosen methods. Due to the research gap, the goal of the empirical study was initially to gain a first-hand understanding of living with HCP. The main research question of the empirical section of this thesis is, therefore, 'How do HCP patients and their families experience their lives with a rare, genetically determined, and chronically-recurrent disease?' Thus, a qualitative, empirical study design was selected to exploratively investigate the experience of persons living with HCP and to understand the relatively unknown disease HCP better.

Research Ethics Requirement

Research ethics requirements, such as the voluntariness of study participation, potential vulnerability of the participants and data anonymity, were observed diligently in the current thesis. Potential study participants were informed in a written and verbal form about the aim and content of the study and data management [Suppl. 1–4]. They were also notified about

the voluntariness of their participation, their right to refuse study participation and that non-participation would have no negative effects for them. In addition, the participants were made aware of the management of the data (access, pseudonymisation, use of citations, deletion of data). After the written and oral information, written informed consent was obtained from all study participants [Suppl. 5–6]. The study was approved by the Ethics Committee of the University Medicine Greifswald [Suppl. 7–8] and is reported according to the COREQ checklist for qualitative research [Suppl. 9].

Sampling Strategies and Study Participants

Concerning the sampling, two purposive strategies were combined: criterion sampling and maximum variation sampling (Palys 2008). The criterion sampling strategy targeted individuals who meet the criterion of having HCP. The sample was restricted to patients who had a personal history of pancreatitis and/or had been tested for the hereditary form (PRSS1 mutations) and/or already had HCP in their family (≥ 2 individuals with pancreatitis in ≥ 2 generations). Patients with other explanatory etiologies for pancreatitis, e.g., alcohol, were excluded from the study. By maximum variation sampling, the goal was to acquire patients who covered the wide spectrum of the disease progression, ranging from typical to extreme cases. Furthermore, the maximum variation sampling targeted further positions and perspectives in relation to HCP. Consequently, unaffected family members and partners were also invited to participate in the study, extending the sample to the parents, children, siblings, aunts, uncles, spouses, and life partners of HCP patients. The composition of the sample aimed at highest variation regarding gender, age, level of education and familial status. The inclusion criterion, at least 18 years of age, applied to all participants.

The close cooperation with a patient organization for patients with HCP and their families in Germany offered great opportunities for sampling. To gain contact to potential study participants, the chairperson of the organization invited the members of the organization for study participation in written and oral form [Suppl. 1–2]. Members who showed interest to this open invitation were informed in detail about the context and objectives of the study by email and mail [Suppl. 3–4]. Those interested were additionally contacted by telephone to clarify any remaining questions. In addition, snowballing sampling was used to find further potential study participants: those contacted through the patient organization were asked

whether they could forward the open invitation to others who could be interested in becoming study participants.

Data Collecting: A Qualitative Triangulation

Qualitative triangulation was chosen to gain a comprehensive and nuanced picture of the experience of living with HCP. The idea of triangulation is to combine different approaches, for example different theories, methods or data to study a phenomenon from different perspectives in order to gain a deeper understanding of it (Rothbauer 2008). Method triangulation in qualitative research can refer to the data collection or analysis. In the current thesis, two methods of qualitative data collection were combined: individual interviews and focus group discussions. The triangulation of these methods made it possible to augment the results of the interview study by the focus group and discuss selected themes in more detail in the group session.

Interview Study

Qualitative individual semi-structured interviews were selected as the method for the interview study because this interview type enables the collection of the individual experience of the interviewed person while relating to the theoretical background underlying the study. The interviews served a two-prong approach: on the one hand, the interviews were intended to encourage the study participants to report their personal experiences with HCP and their method of living with this disease. On the other hand, the interviews sought to ascertain ethical issues in the context of a rare, genetically determined, chronic disease such as HCP. The main research question, 'How do HCP patients and their families experience their lives with a rare, genetically determined and chronic-recurrent disease', was therefore supplemented by questions concerning experiences with genetic testing, biomedical research and patient organizations. Based on these preselected themes and the corresponding literature, the interview questions were developed. Two slightly differing interview guides were designed for the interview study: one for interviews with patients [Suppl. 10] and one for interviews with unaffected family members. Both interview guides were pilot tested, and as only minor modifications resulted, the two pilot interviews were included in the data analysis.

The individual interviews were conducted by Regina Müller (female, PhD student, trained in qualitative research and medical ethics) at the patients' homes or, if a personal meeting was not possible to arrange, via telephone. All interviews were based on the same interview guide, audio recorded, transcribed verbatim and pseudonymized. Field notes were made during and after the interviews.

Focus Group

In addition to the individual interviews, a focus group session with patients as well as life partners was carried out by Regina Müller and a student assistant. The focus group was chosen as further method of data collection because group sessions can help to minimise biases by the researcher, as the participants talk with themselves in the session, not with the researcher. Moreover, since selected themes from the interview study can be explored in greater depth in the group session, the focus group has the potential to strengthen and enrich the previous findings. Furthermore, since the participants can complement or refuse their arguments, the group session is a good opportunity to crystallise ethical issues, which are often implicit and difficult to formulate precisely.

According to the preselected research question, 'What are the ethical and social issues experienced by patients and their families regarding genetic testing for rare chronic diseases such as HCP?', and based on the results of the interview study, the theme 'genetic testing in family contexts' was selected for discussion in the focus group. A semi-structured interview guide was designed with open questions on this theme, slight instructions for the interviewer and input for the group discussion [Suppl. 11]. Selected quotations from the interview study, cards with different roles (e.g., patient, family member, physician) and a lifetime-line were used as input for the debate. Like the interviews, the focus group was audio-recorded. In addition, an assistant wrote a protocol during the session. The audio recording was transcribed in typed form and pseudonymized.

Data Analysis: Qualitative Content Analysis

The transcripts of the individual interviews and the focus group were analysed using content analytical procedures. Qualitative content analysis (QCA), according to Mayring (2014), was selected as the methodology because it is independent of theoretical perspectives and

provides a systematic way of reducing and synthesizing a wide range of data (Julien 2008). QCA is a systematic data analysis technique, whose central idea is to assign categories to text passages through a qualitative-interpretative act (Mayring 2014). The analysis follows a systematic procedure and strict content-analytical rules, combining deductive and inductive category development (Mayring 2014).

According to the objectives of the study, the analysis of the transcripts had two directions: to reveal subjective experiences of the interviewed persons on HCP and identify ethical issues in the material. All transcripts were read, and codes were assigned to each text passage, which seemed relevant according to the research questions and aims. These inductively developed codes were classified into categories. The categories were then categorized into previously developed, deductively formulated themes. In this manner, a coding scheme was created, including codes, categories, and themes. Examples of the category development can be seen in Table 2.

Table 2: Examples of category development.

REPRESENTATIVE QUOTE	CODE	CATEGORY	THEME
Yes, it does restrict me, but not as much as another illness that I would have all the time. Because in my case it only occurs in episodes and then it usually goes away again. (Interview 5)	Episodic occurrence; disappearance; comparison with a cycle	HCP as an ongoing but unstable condition	Unpredictable clinical course of HCP
Especially in the beginning, the first few years, it was unpredictable and because I didn't know what I had, it was like a game of roulette or Russian roulette for me, where I always had to expect that I would be lying down the next day and that I wouldn't know why and was at the mercy of it. (Interview 11)	Unpredictable clinical course; Russian roulette; diseases not known; always expecting an attack; reason for the attack unknown; at the mercy of the disease	Unpredictability; not knowing; fear of attacks; helplessness	Unpredictable clinical course of HCP
Well, for me, it means restrictions in many areas, you can't do the things the way you want but, on the other hand, it's also a disease that you can definitely live with. (Interview 15)	Restrictions in general; effects in many areas; not being able to do things as wanted	Restrictions	HCP as a devastating experience

Reprint in slightly adapted form from Müller et al. 2021a.

The transcripts were analysed using the software program MAXQDA12. As the qualitative analysis is a cyclic process, the coding scheme was regularly discussed in team meetings and accordingly modified. Rater influence was minimized by frequent team discussions during the coding process and by including researchers with different professional backgrounds in the data interpretation.

Ethical and Conceptual Analysis

Based on the empirical findings, ethical and conceptual analyses were conducted. There is no single way to conduct an ethical analysis; instead, a variety of methods in bioethical literature exists. Often ethical frameworks or certain ethical theories, such as principlism or utilitarianism, are used. In this thesis, undertaking an ethical analysis means identifying the ethical issues in the research context, mapping them, revealing research gaps, and giving orientation for ethical decisions. Different frameworks and concepts are used for the theoretical background for the ethical analysis because of the wide-ranging ethical questions HCP reveals. For example, in the section on living with HCP, the 'Ethics of Chronic Illness' provides the framework; meanwhile, in the section on genetics issues in the family context, the 'Ethics of Genetic' and the 'Ethics of Families' form the background.

Conceptual considerations are closely linked to the ethical analysis in this thesis. Conceptual analysis is one of the main traditional methods of philosophy and ethics. Its basic idea is that ethical questions '[…] can be answered solely on the basis of one's grasp of the relevant concepts' (Horvath 2021). It is a method of inquiry in which complex systems of thought are assessed by 'analysing' them into simpler elements and revealing their relationships (Baldwin 2005). The results of a conceptual analysis can provide definitions or logical analyses of the necessary and sufficient conditions for a phenomenon, term or entity (Horvath 2021).

In the current thesis, the section on the moral responsibility of PAOs is particularly based on conceptual analysis. Concerning the research question 'What is the moral responsibility of a patient advocacy organization?', responsibility is understood as a relational concept and 'broken down' into four single reference points: someone (the subject) is responsible to somebody (the addressee) for something (the object) regarding normative criteria (normative criteria) (Figure 1). This four-point relationship will be applied to PAOs, each of the relata and their complex relations will be discussed and the underlying normative values will be revealed. This conceptual analysis allows for the structuring and analysis of the complex situations with which PAOs are confronted and which are characterised by questions of responsibility. To illustrate the conceptual considerations, the four-point relationship is exemplarily applied to a concrete situation of a PAO and supplemented by the findings of a systematic review.

Systematic Review of Reasons

Once the responsibility of PAOs had been analyzed, a systematic review of reasons was used to complement the conceptual considerations with reasons concerning the involvement of patient groups in drug research. Systematic reviews are traditionally a technique in medical research to evaluate the effectiveness of a clinical intervention by a systematic and comprehensive review of the existing literature with minimal bias (McDougall 2014). In recent years, the technique has also been applied to bioethical literature, and different models to review normative literature were developed (McDougall 2014). The common idea is to identify and analyze all relevant publications concerning a particular normative question in a comprehensive and systematic manner. The approach of a systematic review of reasons addresses '[…] the factual question of which reasons have been given when discussing the ethical question and how they have been used' (Strech et al. 2012). As a result, a systematic review of reasons can identify gaps in the literature, show potential for further research and help to guide decisions in practice of medicine, research and health policy (Sofaer et al. 2012). Strech and Sofaer (2012) developed a model for conducting a systematic review of reasons including different steps, from the formulation of the review question and the eligibility criteria to the identification of the relevant literature, data extraction and synthesis. This review technique was selected to acquire detailed information on the ethical arguments discussed in the literature concerning the involvement of PAOs in drug research. The specific example of PAOs' involvement in drug research was used to complement the discussion on PAOs' responsibility more concretely. A systematic review of reasons was conducted and is reported according to the PRISMA Statement [Suppl. 12].

Inclusion Criteria, Databases and Study Selection

Two search terms were defined for the review. 'Patient group' was defined as '[…] any group consisting of patients and/or patient advocates which consistently promotes patients' interests' (Rach et al. 2020). 'Drug research' covers '[…] all phases of research and development of a medicine product from target identification to clinical Phase III studies' (Rach et al. 2020). Based on these two search terms and their synonyms, a search strategy was built and the databases PubMed and Web of Science were utilized to gather results. The

search string for PubMed can be seen in Figure 2. There were no restrictions regarding the period or the publication types. The languages were restricted to English and German.

Figure 2: Search string for PubMed.

(((pharmaceutical[Title/Abstract] OR drug[Title/Abstract] OR drugs[Title/Abstract] OR medication[Title/Abstract] OR medicament[Title/Abstract] OR "medicinal product"[Title/Abstract] OR medicines[Title/Abstract]) AND ("research"[MeSH Terms] OR research[Title/Abstract] OR Development[Title/Abstract] OR design[Title/Abstract] OR discovery[Title/Abstract] OR evaluation[Title/Abstract] OR approval[Title/Abstract])) OR "drug discovery"[MeSH Terms] OR "drug evaluation"[MeSH Terms] OR "drug approval"[MeSH Terms]) AND (("self-help groups"[MeSH Terms] OR self help group[Title/Abstract] OR self help groups[Title/Abstract]) OR (patient organisation[Title/Abstract] OR patient organisations[Title/Abstract]) OR (patient organization[Title/Abstract] OR patient organizations[Title/Abstract]) OR (patient association[Title/Abstract] OR patient associations[Title/Abstract]) OR patient advocacy[Title/Abstract] OR "patient advocacy"[MeSH Terms] OR patient involvement[Title/Abstract] OR patient engagement[Title/Abstract] OR patient Participation[Title/Abstract] OR "patient participation"[MeSH Terms])

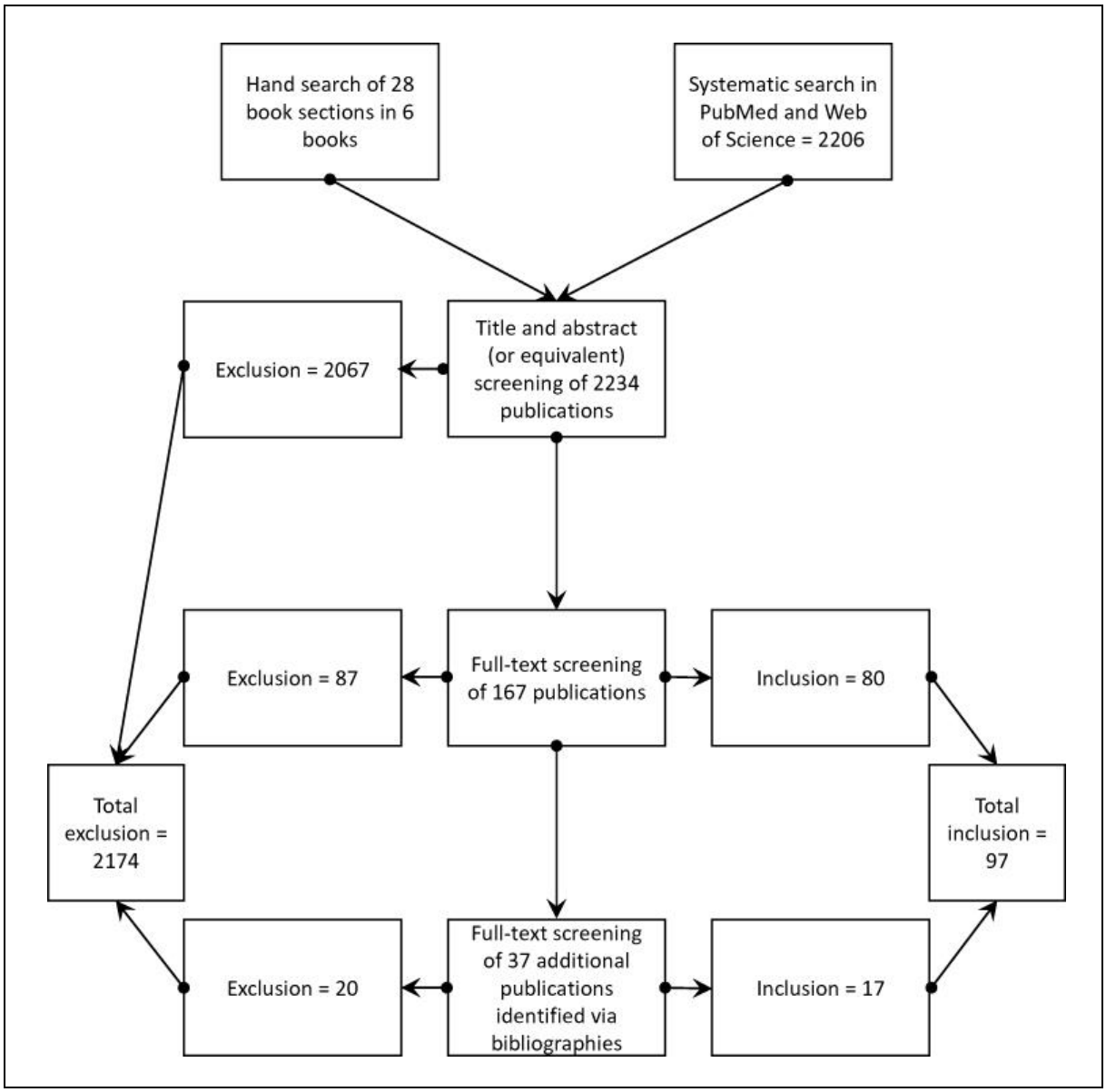
Reprint from Rach et al. 2020.

All publications that covered the defined research terms and fulfilled the inclusion criteria were screened, first by title and abstract screening, then in full text. To minimize uncertainties and biases, the preliminary results of the review were discussed in team meetings. The results of an additional manual search in books and of the screening of the bibliographies of the relevant publications were also included in the review. The study selection can be seen in Figure 3.

Data Extraction and Qualitative Synthesis

The included publications were analysed regarding the involvement of patient groups in drug research with the technique of QCA, according to Mayring (2014), and the software program MAXQDA12. All publications were screened for reasons (for, against or ambivalent), which were inductively extracted and assigned with codes. These inductively developed *narrow reasons* were included in deductively developed *broad reason* types. As a result, a coding scheme was developed, discussed and revised in team meetings. All publications were screened a second time with the final coding scheme to ensure the correct assignments of the codes.

Figure 3: Flow chart of the study selection.



Reprint from Rach et al. 2020.

RESULTS

Selected study results will be presented in the following, starting with the experience-based findings classified into the three main themes (1) experience of living with a chronic, but unstable disease; (2) experience with genetic testing in the family context; and (3) experience with patient organizations. The empirical findings, particularly on the third theme 'patient organizations', will be supplemented by the results of the conceptual analysis and the review. The results are presented in the form of a summary, structured according to the relevant publications. For the most parts, the results are in accordance with the result sections of the respective publications, but some parts are supplemented with unpublished data.

Results of the Qualitative Study

The qualitative study was conducted between July 2017 and November 2019 in Germany and included 24 individual interviews and one focus group. Originally, 26 participants were enrolled in the interview study, but two participants declined to be interviewed for personal reasons. Of the remaining 24 interviews, 17 were with patients, 7 with family members. 22 of the interviews were conducted at the participants' homes, two by telephone. The interviews lasted an average of 44 minutes (median: 43 minutes), ranging from 16 to 91 minutes.

Initially, two focus groups were planned, but the second group did not attain enough participants. As the potential participants were reluctant to discuss their experience with the sensitive topic of genetic testing in front of others, the first group consisted of a relatively small number of four participants (2 patients, 2 life partners). The group discussion was conducted at the annual conference of the patient organization for patients with HCP and their families in 2019 and lasted 75 minutes.

The study included patients in different stages of the disease, from patients who had symptoms since their birth or childhood to patients who became symptomatic in adulthood. One patient was in an acute period of the disease during the interview study. Interviewed family members covered parents, children, siblings, aunts, uncles, spouses and life partners. Different but interwoven familial relationships are covered in the study. For example, one study participant was the partner of a patient and, at the same time, the parent of an affected child. To manage these complex relationships, the participants were asked to formally assign

themselves a role, resulting in the three categories: patient, partner and parent. Most participants were older then 30, married and had children. Most were well educated and worked at the time of the interview study. Additional characteristics of the participants can be seen in Table 3.

Table 3: Participants' characteristics (interview study and focus group).

		PATIENTS (n = 19)	RELATIVES (n = 9)	TOTAL (n = 28)
Age		20-70 Median: 49	33-78 Median: 53	20-78 Median: 52,5
Age groups	18-30	2		2
	30-50	8	2	10
	50-70	8	6	14
	70-90	1	1	2
Gender	Male	7	5	12
	Female	12	4	16
Education	A level	11	4	15
	Secondary school	7	4	11
	Other	1	1	2
Employment		15	6	21
Marital status	Single	5		5
	Married	12	8	20
	Living together	2	1	3
Having children		12	7	19
Genetically tested		11		11
In acute episode		1		1
Member of the patient organization		12	4	16
Relationship of the relatives to the patient	Parent		3	3
	Spouse		6	6

Selected study results regarding the impact of HCP on the lives of patients and their families will be presented in the following, oriented to the three main themes (1) experience of living with a chronic, but unstable disease; (2) experience with genetic testing in the family context; and (3) experience with patient organizations. Since HCP patients and their families are a relatively small group in Germany, the role (patient, relative), age and gender of the interviewed person will not be indicated in the following quotes to guarantee data anonymity.

Experience of Living with a Chronic, but Unstable Disease

(Mueller R, Aghdassi AA, Kruse J, Lerch MM, Rach C, Simon P, Salloch S. 2021)

The study participants described HCP as an ongoing, but unstable disease. The participants could not predict the course of the disease: they could report neither when nor how long the

acute phases of the disease would occur. Some participants spoke about acute phases lasting a few days, others reported acute phases of several weeks. Some participants described more than one phase in short periods; others experienced no phases for several years. Despite these differences, most participants reported that the acute phases recurred and compared this to a cyclical process.

> *We don’t know when it will come because it is so, well, unpredictable. It can go bad; it can go well for a long time. [Interview 17; Müller et al. 2021a]*

> *You just got over it, and then it started again. [Interview 15; Müller et al. 2021a]*

Concerning the acute phases, the participants reported phases ranging from mild to very severe. The latter were described as periods in which the participants could not eat and drink, had extreme pain and often had to go to the hospital. In these phases, the participants described an immediate loss of energy and perceived themselves as extremely weak. As there is no treatment, the extreme weakness and unbearable pain brought the participants to their physical and psychical limits. Because the severe phases took the participants out of their lives, they were described as disruptive experiences. The acute phases were devastating not only for the patients themselves but also for the family members.

> *This [the acute phase] is really a point where you think, well, it can’t go on. [...] and you can’t really go back into life because you always have some pain and so on and you don’t know what’s going on now. That worries you. [Interview15; Müller et al. 2021a]*

> *Well, it's just awful. There is no word for it. It's just really bad, [...] I don't know anything similar, it's definitely the worst thing I've experienced so far. [Interview 19]*

Due to the acute phases, the participants reported restrictions in their lives, for example, regarding school, work and family life. As the participants could not foresee the acute phases, they described many uncertainties and difficulties in planning, for example, regarding travel. As the occurrence of the acute phases could not be prevented, the participants additionally reported feelings of powerlessness and helplessness. Some participants expressed that they felt themselves at the mercy of the disease. Due to the unpredictability of the disease, the participants are always vigilant and prepared for acute phases. In particular, family members stated that they maintain increased attention to the patient and their wellbeing and were permanently alert.

Well, it's not always easy because, for example right now, I can't do my job and that's, well, limiting. [Interview 5]

[HCP] means for me, always being restricted in some ways. [Interview 23]

You can't foresee it, and it's hard to plan for it. [Interview 12]

I always was afraid of getting an attack, especially in the beginning, in the first few years, it was unpredictable and because I didn't know what I had, it was like Russian roulette for me. I always had to expect that I would be sick the next day, but I wouldn't know why, and well, I would be at the mercy of it. [Interview 11]

At the same time, the participants reported long episodes in their lives, in which there were no acute phases, whereby the disease was unremarkable. Referring to these phases, the participants often relativized foresaid restrictions and difficulties due to the disease. Concerning the periods without acute phases, the participants expressed themselves as healthy and described their life as normal compared with the lives of other people. However, even though the disease disappeared, the participants described it as inevitable part of their lives, which means that the disease had always been part of their lives and would ever be there.

Actually, I'm not ill. I don't feel sick, on the contrary, I feel healthy. [Interview 19]

It's hard for me to say, yes, I'm ill, because it's not present, at the moment [...] I'm a normal teenager. [Interview 5]

Well, it does restrict you, yes, but not as much as another illness that you would have all the time because it only occurs sometimes, and then it usually goes away again. [Interview 5]

Referring to the shifting phases of the disease, the participants reported experiences of being misunderstood, reduced to the disease and associated aspects of it and discriminated against, even in periods without symptoms. Some participants stated that others notice primarily their disease, not the person or the current context of the disease. One participant reported, for example, that in the context of a medical check-up, other health issues were overlooked as the healthcare professionals focused solely on HCP. Although many participants saw themselves as experts regarding the disease, they often did not feel understood, especially in the medical context. Some participants mentioned expectations from third parties that comes with the attribution of the disease, for example, that they should eat healthy or avoid (risky)

sports. Discriminatory comments were also reported in the context of the participants' working lives.

> *It's not necessarily the illness itself that is the problem […] So, if I just go to a doctor now and say I have the disease, then he just looks at me at this point and at nothing else. I always say, yes, but I also have other things. That is, I think, very, very important. [Interview 5; Müller et al. 2021a]*

> *It's seldom accepted by doctors that patients and their relatives know how to treat the disease. In general, as a patient, you are being seen as stupid and there's massive discussion every time you are in the hospital for an acute episode. [Interview 10]*

> *I wasn't allowed to do many things […]. My parents always put a stop, early on, on the advice of the doctors, when it came to sports, or things like that. That's why I would say, backward-looking, it changed a lot, because many things simply didn't happen, for example, sports, there was never any possibility for me doing competitive sports or anything like that. [Interview 19]*

> *So, if I imagine, I would meet myself and see that she does everything and is just normal, and in the next moment she's in hospital for several weeks, I probably wouldn't understand that. And that's the biggest problem. Most people don't understand. […] They don't understand the difference. It's always a bit problematic. [Interview 5]*

Experience with Genetic Testing in the Family Context

(Mueller R, Aghdassi AA, Kruse J, Lerch MM, Simon P, Salloch S. 2021)

Genetic testing was identified in the individual interviews as a complex, but important issue for the patients and their families. It was selected, therefore, as topic for the focus group. In the following, selected results, particularly from the group discussion, will be presented, focusing on the participants' experience with genetic testing in childhood, within the family and regarding family planning.

The participants in the focus group discussed whether genetic testing for HCP in childhood would be useful. They were unsure how to assess the optimal time for testing. Arguments for and against genetic testing in childhood were raised and different ages for testing were discussed. Most participants were reluctant to support testing immediately after birth or in early childhood as, in their opinion, children at such an early stage of development cannot decide for themselves. Lacking capabilities to understand and decide and missing life

experiences were mentioned as relevant aspects against testing. However, first symptoms of HCP were seen as a key factor in determining the right time for testing. Some participants recommended genetic testing in adolescence as the testing could lead to certainty about the disease and its origin and have reassuring effects. In the end, the decision for or against genetic testing was considered by the participants as so individual that its optimal time could not be determined, in general.

> *The right time for testing? I would say, early in [adult] life because then it brings more certainty that you know where it comes from. [Focus group; Müller et al. 2021b]*

> *As I said, it's very, very difficult, when you are a kid. As a kid, you are inexperienced anyway. [Focus group; Müller et al. 2021b]*

The participants also controversially discussed the role and responsibilities of parents. Some participants recommended genetic testing, as in their view the genetic information was important for the parents to react appropriately to the disease. In contrast, other participants highlighted the potential negative consequences of the test results. They argued that the genetic information could lead to fear and adverse reactions by the parents. Restrictions, control and surveillance of the child's development were discussed as examples.

> *I think it's also very important […] how the parents react at that moment. Do they panic 'we have to do this and that', or do they deal with it very calmly and sensibly? I think this is very important, even for the rest of your life. It shouldn't be underestimated. Of course, taking precautions, but there are, I say, these 'helicopter parents': 'Rather not, better not, not at all, and no, you aren't allowed to go to friends and eat elsewhere', although there's nothing yet. [Focus group; Müller et al. 2021b]*

Some participants reported that families had done genetic testing together, which means that they had an appointment for testing together, and all family members did the test. A main motivation for the individual family members to do the test together was the interest in knowing the carrier of the disease. Some articulated the wish to support the affected person, and some expressed, in this context, a 'sense of togetherness'. Arguments raised by the participants against testing together were that testing together was useless as the test had little or no consequences. In addition, some participants emphasized the right of not knowing. Although most participants stated that they were interested in the opinion of their family

members, most of them highlighted that the decision for or against testing remains an individual decision.

> *Everyone else is, of course, asked for their opinion, or perhaps simply what they would do, so that I can hear what they have to say. I want to hear what they have to say, but, at the end of the day, I'm the person who makes the decision. [Focus group; Müller et al. 2021b]*

> *Well, there is only one person who decides: that is the patient. End of story. [Interview 10]*

Genetic testing and information were relevant factors for the participants in the context of family planning. The wish to have a healthy child was repeatedly expressed in the discussion and the participants emphasized that as parents they want the best for the child. Especially the female participants reported feelings of fear and guilt of transmitting the disease to their children.

> *I felt this between my mother and me, and I feel this now between me and my daughter. And, you're blaming yourself as a mother. You sit there and think, God, I just want the best for my kid, and you give her an illness like that. What kind of mother am I? […] I certainly felt bad about it, some fear, despair, and I think my mother had felt the same. [Interview 11]*

The participants discussed the relevance of genetic information in decisions for or against children. According to some participants, transmitting the disease is a form of harm and it is not acceptable to harm someone else, especially a child; thus, they were against having children. In addition, the burden for the families was addressed. Some participants raised the concern that having an ill child would be too burdensome for the family, especially for the mother. In the context of these arguments, abortion was discussed as an option. By contrast, some participants argued that HCP was not burdensome enough to refrain from having children along with the uncertainty if the child would get the disease. This uncertainty was a difficult and burdensome aspect for the participants in the decision-making process, and some described themselves as powerless in this context.

Experience with Patient Organizations

Because of the often-mentioned feelings of powerlessness and uncertainty, the participants were asked for their experience with patient organizations. Although most of the participants

were members of the patient organization for patients with HCP and their families in Germany, they described different reasons why they became members of the organization. The motivations for active membership were to help each other, support affected family members, especially their own children, educate themselves (about the diseases), learn new perspectives and network. Study participants who were not members, or at least not active members, of an organization mainly stated that the diseases did not directly affect them, and they, therefore, had neither a need for help nor saw any personal benefits in participating in such organizations. Some participants reported that they did not the resources for an active participation; others stated that they did not want to address their disease.

The participants described the role of the patient organization in three dimensions: 1) help and networking; 2) information; and 3) further support. According to the participants, the main function of the organization was to enable self-help, mutual support and networking. It was emphasized that the organization helped them get connected to relevant (health) services, other individuals and families affected. In this context, the participants described feelings of 'togetherness'. In addition, the organisation of group meetings and conferences was mentioned as a helpful feature of the organization.

> *Of course, if I have a disease, [and] nobody can help me, and then there is someone, who tells me: hey, I have the same. I did this and that helped me, then this is very helpful. [Interview 10]*

Furthermore, the participants highlighted that the organization provided secure and up-to-date information, such as new research results, especially compared to information on the internet. It was emphasised that the organization delivered different types of knowledge, for example, information by experts such as scientists but also knowledge that is relevant for the participants' everyday life, for example, information regarding insurances. The participants also praised the organization for writing recommendations and helping to make the disease more visible, in general.

> *The more people you inform, the more they talk and share with each other, and the more it helps. [Interview 4]*

> *I find that always very exciting: different opinions from different disciplines [...]. These different opinions help us, the patients, [...] we say, yes, there I see myself more, there I see myself not so much and then we get in touch with the experts. [Interview 4]*

Although many of the participants had only little contact with the patient organization, they highlighted the support of the organization in the background and described the organization as a safety net on the side-line. The opportunity for immediate and individual help was emphasized. Knowing that there is a contact person in the case of acute need was described as helpful and reassuring.

> *If I need help, no matter what, I can call them, no problem. I have that in mind, and that's enough. [Interview 11]*

Although the participants stated positively that engaged persons and experts were concerned with the disease within their work in the organization, they demanded more support, for example, directly after diagnosis. In addition, the participants expressed the wish that the organization should make HCP more visible in society.

Results of the Conceptual Analysis

(Mueller R, Rach C, Salloch S. 2021)

The conceptual analysis shows that PAOs, understood as collectives (French 1982), fulfil certain aspects of moral agency, such as intentionality, and can consequently bear moral responsibility. Depending on their size and degree of professionalization, PAOs can thus, in principle, be *the subject* of moral responsibility. If PAOs are the subjects of responsibility, what are they responsible for? Despite the diverse tasks attributed to PAOs, their common goal is relatively clear: to represent those affected and stand up for their rights (Epstein 2008, Wehling et al. 2015). Patient representation and advocacy can, therefore, be seen as *the object* of the PAOs responsibility. The object of PAOs' responsibility remains to some degree unspecified because the concrete forms and implementation of patient representation are manifold, ranging from interaction with individual patients to public communication and political and industry engagement. While this view does not yet provide concrete ethical obligations, it highlights the moral character of PAOs' engagement and reveals the underlying values – representing patients and advocating for their interests. Responsibilities that are more concrete, for example, regarding certain cooperation partners, can build on these basic values.

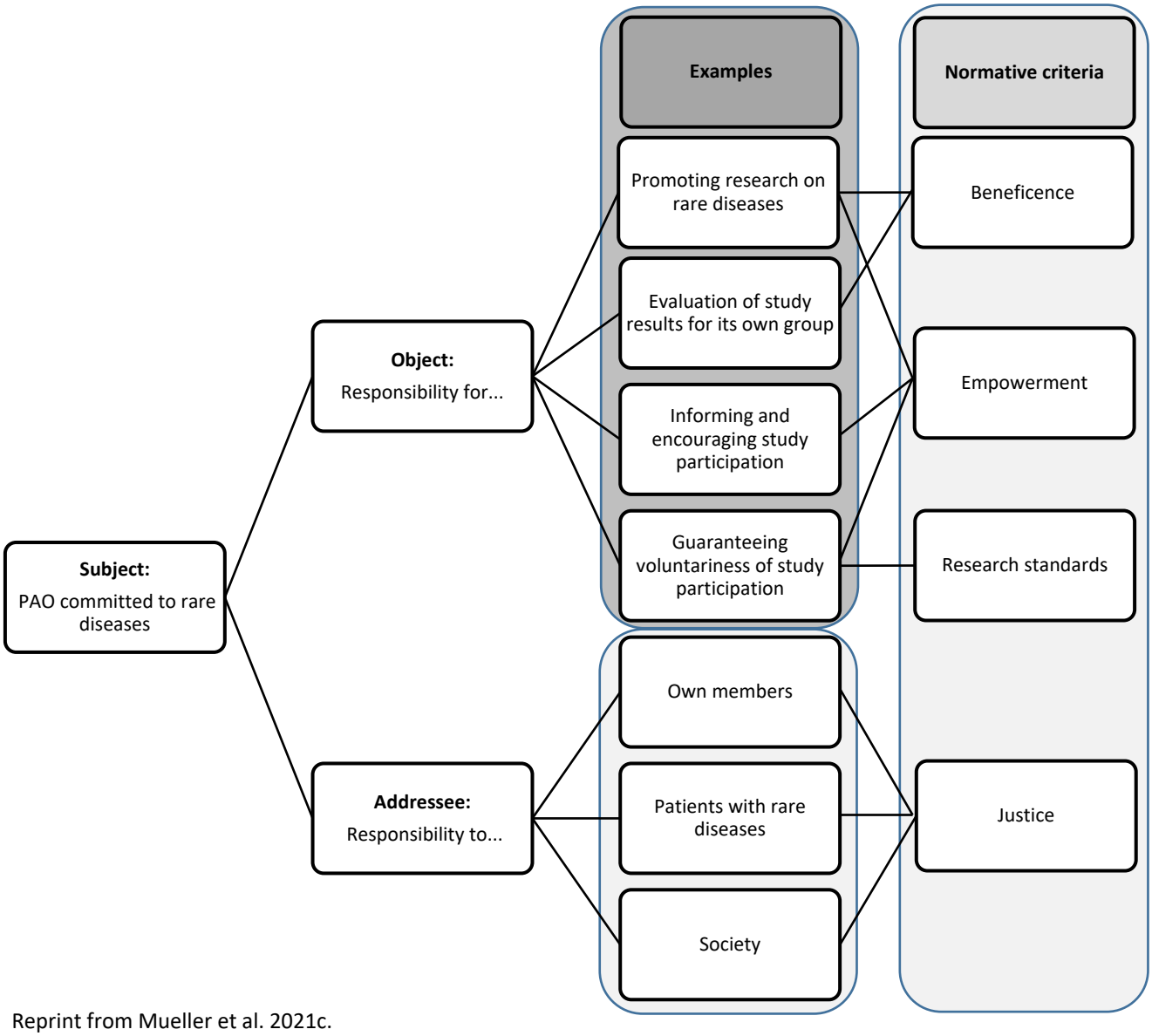
Having identified what PAOs are responsible for, the question of the addressee remains. Given their advocacy role, it seems acceptable that the addressee of PAOs' responsibility is primarily their targeted (patient) group. However, only considering distinct groups of patients can be too short-sighted in some situations. Issues regarding genetic contexts, for example, might go beyond the patients and affect other individuals or groups. As this example shows, PAOs are frequently confronted with issues of ethical significance that not only affect their own members but also other groups. It is, therefore, within the responsibility of PAOs to consider the ethical implications of their activities in a broader social context.

If PAOs are assigned responsibility, a normative standard is needed. Typical standards for attributing responsibility are, for example, legal frameworks or ethical principles. Which standard is chosen depends, inter alia, on the activities being judged and the type of responsibility (e.g., legal, political or moral) being considered. In the context of PAOs, various legal and political frameworks, but also the PAOs' own constitutions and the ethical principles of justice, beneficence and empowerment contained therein, can be used as normative standards. Which standards are used may vary depending on the circumstances in which the PAOs find themselves.

For example, PAOs that want to support research may find themselves in difficult decision-making situations, which are characterized by questions of responsibility. The proposed framework of responsibility can serve as a practical tool to structure these morally difficult situations. Imagine a PAO, that is committed to rare diseases, receives the invitation to join a clinical trial carried out by a public research institution together with a pharmaceutical company. The PAO could support the study by inviting its members to participate. However, the PAO's officials are unsure whether they should recruit participants for the study. They are questioning for what and to whom the PAO is responsible for in such a situation, and which normative principle can justify this responsibility. As shown elsewhere in more detail (Müller et al. 2021c), the outlined framework can help to structure this situation and provide orientation. Figure 4 illustrates the application of the four-sided model of responsibility to this exemplarily situation. As the application shows, the interpretation of responsibility regarding the PAO's involvement in research is multifaceted and the relata of the model are often interwoven. These ambiguities can be minimised by a precise specification about who is responsible, for what, to whom and on the basis of which ethical standard. An accurate

application of the model can help with structuring the situation, clarifying the underlying ethical principles and, thus, contributing to the solution of the question of responsibility.

Figure 4: PAOs' responsibility regarding research.



Reprint from Mueller et al. 2021c.

Results of the Systematic Review

(Rach C, Lukas J, Mueller R, Sendler M, Simon P, Salloch S. 2020)

The results of the systematic review of reasons can complement the experiences of the participants regarding the role of patient organizations and enrich the discussion on the PAOs' responsibility at the conceptual level. The review searched for arguments for and against the involvement of patient organizations in drug research. Of 2.271 identified publications, 97

publications were included in the analysis. The included publications cover journal articles and book chapters, ranging from 2001 to 2019, and are written in English. A table of all included publications can be seen in Supplement 13.

As shown elsewhere (Rach et al. 2020), the data extraction resulted in a total of 124 reasons, of which 91 (73.4%) were reasons for the involvement of patient organizations in drug research, 30 (24.2%) were reasons against and three reasons (2.4%) were ambivalent. The reasons were classified around the six main categories: Resources, Collaboration, Science, Patient community, Ethics and Public Relations (Table 4). A detailed list of all reasons, the number of publications each reason occurred in and how the reasons were used (for, against, ambivalent) can be seen in the corresponding publication by Rach et al. (2020).

The review revealed a broad variety of reasons with a high number of positive arguments. Many publications included in the review have the tendency to discuss the topic rather superficially and advocate the inclusion of PAOs in research without much critical reflection. The reasons for this imbalance and the underrepresentation of contra arguments in the literature is discussed elsewhere (Rach et al. 2020), but the results of the review can complement the study participants' experience in this regard and the analysis of the PAOs responsibility.

Table 4: Categories of the review.

CATEGORY	DEFINITION
Resources	Since resources are limited, many reasons relate to the question of whether PGs can acquire, distribute and use resources needed for the research process effectively. Resources discussed include financial investments, research samples, scientific data and time.
Collaboration	The creation of new acquaintances and connections between researchers and other stakeholders was generally rated highly for the research process. PGs play a key role in establishing these collaborations.
Science	This category deals with all reasons concerning quality, conditions, aims and conduct of scientific studies. There are ways in which PGs can influence these parameters either positively or negatively. Setting research agendas is one of the topics mentioned most frequently in this BRT.
Patient community	Reasons regarding the quality of patient representation by PGs can be found in this BRT. Possible contributions of patients based on their unique experiences and potential benefits and risks which affect patients directly are also discussed.
Ethics	Justification and fairness of research with the involvement of PGs are major reasons in this BRT. PGs' handling of ethical issues is also considered.
Public relations	The ability of PGs to promote research-friendly political surroundings and shape the public perception of drug research is subject to reasons in this BRT.

PG = patient groups; BRT = Broad reason type. Cited in slightly modified form after Rach et al. 2020.

DISCUSSION

In the following, the discussions from the main publications are presented in the form of short summaries. The summaries are based on the discussion section of the respective publication and partly supplemented with new thoughts.

Pathologization as Ethical Aspect of Unstable Chronic Diseases

(Mueller R, Aghdassi AA, Kruse J, Lerch MM, Rach C, Simon P, Salloch S. 2021)

The results of the qualitative study show the unstable and unpredictable character of HCP. The participants reported varying experiences, ranging from very harmful to positive. The disease has different and, in some cases, far-reaching impacts on the quality of life, covering physiological and psychological suffering and effects on the daily working, social and family life. Further studies confirm these variations in the course of the disease, its wide range of impact and the associated feelings of uncertainty, fear and helplessness due to the unpredictability of the disease (Cronin and Begley 2013, Boije et al. 2019, Shelton et al. 2020).

Referring to the acute phases, HCP was described as disruptive experiences by the study participants. However, the concept of biographical disruption by Burry (Bury 1982) does not completely cover the experience of patients with HCP since the participants in the current study spoke not about one specific disruptive point in their life's, but about recurring disruptive elements throughout their entire life spans. Although the acute phases were described as repeating, disruptive experiences, the participants described the disease as invisible for some periods of time and their lives with HCP in these periods as normal. As debated elsewhere (Müller et al. 2021a), this constantly shifting experience of HCP is adequately covered by Paterson's 'shifting perspectives model' (2001) of chronic illness.

Due to the changing character of HCP, the participants reported the experience of being reduced to the disease and labelled as ill, although they considered themselves as healthy. As shown elsewhere (Müller et al. 2021a), this misattribution can be understood as a form of pathologization (Sadler et al. 2009, Fassin 2011, Sholl 2017). Being perceived as ill was described by the study participants as problematic because this attribution can come with expectations regarding the patients' behaviour, assignments of guilt, stereotypes, depersonalization and objectification (Müller et al. 2021a). Diverging perceptions and

consequently diverging expectations can lead to conflicts and far-reaching problems for those affected, for example, in the healthcare system (Holmen 2020). The awareness of healthcare professionals for the shifting character of HCP and a patient perspective that may differ from the own perspective is, therefore, central for adequate and individualized care. Healthcare professionals can focus on the patients and respond to their different needs in the distinct phases to meet the changing character of the disease and to avoid reduction or pathologization. A better understanding of the shifting character of HCP and the associated problems can help healthcare professionals to tailor the care to the needs of those affected and to provide individualized support. In addition, the knowledge of the shifting character of the disease can prevent patients from being pathologized and help healthcare professionals to better discuss situations of pathologizing. Hence, it is important to integrate the knowledge of the shifting character of chronic diseases, such as HCP, and the associated ethical problems of reduction and pathologization into the scientific and practical medical education.

Genetic Information in Family Contexts

(Mueller R, Kruse J, Lerch MM, Aghdassi AA, Simon P, Salloch S. 2021)

The study shows that genetically determined conditions, such as HCP, (predictive) genetic testing and genetic information, are complex issues in familial contexts that come along with uncertainties and several ethical issues. Normative aspects revealed by the study and discussed in the bioethical literature on genetic testing are individual autonomy and informed consent (Soden et al. 2012), reproductive choices (Decruyenaere et al. 2007, Biesecker 2019, Werner-Lin et al. 2019) and information sharing within the family (Forrest et al. 2002, Forrest et al. 2008). As with other hereditary diseases, the study participants particularly described the uncertainties that come with the genetic information as burdensome, for example, regarding family planning. The study demonstrates that the patients and their families find themselves often in situations of uncertainty caused by the hereditary character of the disease and, furthermore, that they need support in dealing with these uncertainties, for example, in decision-making situations.

Healthcare professionals can support individuals and families in the decision-making processes better if they are aware of these difficulties. The setting of the genetic counselling is a key opportunity for practitioners to help patients and families to manage the reported

uncertainty (Fisher et al. 2016). Different approaches, for example, uncertainty management theories, can help to illuminate and address the various types of uncertainty those affected face (Fisher et al. 2016). Studies showed the relevant role of genetic counselling for families in managing emotionally challenging risk-related uncertainty and the important role of communication in the management of these uncertainties (Fisher et al. 2016). The important role of counselling in the specific context of HCP is already emphasized in several contributions, for example, in the guidelines of the International Association of Pancreatology (Applebaum et al. 2000, Ellis et al. 2001, Fink et al. 2007). In addition, communication strategies and psychological care should be key components in the support and counselling of patients and their families, tailored to the needs of these patients through further empirical research and addressed in greater detail in the medical training of healthcare professionals.

The counselling guidelines, for example, of the International Association of Pancreatology (Ellis et al. 2001), aim, among others, at supporting patient autonomy in the decision-making process, which means ensuring the concept of informed consent and respecting the individual choice developed in the genetic counselling (Ellis et al. 2001). Although patient autonomy and informed consent are central ethical concepts in the setting of genetic decision-making and counselling, the findings of the current study also raise awareness of the familial contexts: familial relationships and dynamics can have a major impact on individual decisions regarding genetic testing and vice versa (Gilbar et al. 2009, Gilbar and Barnoy 2012, Cowley 2019). However, in the context of health (care), families and their possible wide-reaching influence are often overlooked or assumed uncritical (Price et al. 2015). In contrast, this study underlines that families are a central part of health, illness and health-related ethical choices. A better awareness of these relational contexts can help healthcare professionals with integrating the families into the management and decision-making process in the context of hereditary conditions. Social workers, psychological caregivers and peer or patient groups can be further important sources of support for patients and their families confronted with the difficult decisions and uncertainties regarding genetic testing and information.

Roles and Responsibilities of Patient Organizations

(Mueller R, Rach C, Salloch S. 2021; Rach C, Lukas J, Mueller R, Sendler M, Simon P, Salloch S. 2020)

Because of the discussed difficulties of living with a chronic but unstable disease and the uncertainties due to the genetic character of HCP, some patients and family members of the current study are members of a patient organization for HCP in Germany. The interview study shows the broad range of tasks that the study participants attributed generally to patient organizations: from mutual support to building networks and improving the visibility of the disease in the public. As shown elsewhere (Mueller et al. 2021c), these are typical tasks of PAOs. However, given the wide-ranging assignment of tasks, the question arises, what roles do PAOs have and what responsibilities do they bear. The conceptual analysis shows that PAOs can, in principle, be seen as responsible for patients' representation and advocacy, primarily towards their own (patient) group but secondarily in a broader social context. Concerning the responsibility of PAOs, the bioethical literature often addresses PAOs participation in biomedical research (Schicktanz 2015, Wehling et al. 2015). By using the involvement of PAOs in drug research as an example, the systematic review of reasons shows the broad range of arguments for and against potential collaborations between PAOs and medical research (Rach et al. 2020). Since the arguments are very contradictory, no general recommendation can be derived from the review; instead, an individual evaluation of each organization and its specific situation must be carried out. As shown in the conceptual analysis, responsibility as a relational concept can serve as a tool to structure situations characterized by questions of responsibility (Müller et al. 2021c).

Together, the results of the qualitative study, the systematic review of reasons, and the conceptual analysis contribute to a better understanding of the roles of patient organizations in the specific context of HCP, but also in current bioethical discussions and the healthcare sector in general. A better understanding is important for PAOs themselves, given the constant challenges they face. For example, regarding representation in health policy (Baggott and Jones 2018, Jongsma et al. 2018), the knowledge of their own roles and responsibilities can help PAOs find their own positions, represent their members adequately and meet the expectations attributed to them. The awareness can help PAOs find their own viewpoint in difficult decision-making situations and establish clear relationships, especially with regard to critically discussed collaborations, such as industrial (McCoy et al. 2017, Rose et al. 2017) or political co-operations (Schicktanz 2015, Ehrlich et al. 2019). Conversely, the knowledge can

help biomedical researchers, policy makers and commercial stakeholders to better understand the roles and responsibilities of PAOs and develop fruitful collaborations with them. As the findings of this study helps to structure situations and clarify the underlying ethical principles and hence gives orientation in complex situations of responsibility, further research can investigate whether the results of this study can be transferred to other groups in the healthcare sector, such as small peer groups but also large civil society organizations.

Strengths and Limitations

The aim of the current thesis is to gain a comprehensive understanding of living with HCP and the normative issues which accompany it. Considering this goal, one strength of the present study is the combination of different methodologies: qualitative empirical research methods, ethical and conceptual analysis, and a systematic review of reasons. This combination of approaches allowed for a comprehensive analysis of the ethical and social issues in the context of HCP. Despite the wide range, the results also have a certain depth. In particular, the use of qualitative semi-structured interviews in combination with the focus group enabled an in-depth insight into living with HCP. In addition, by involving relatives, more details could be revealed than by analysing solely the data of the patients.

One limitation of the qualitative study is that it is a onetime study, without a longitudinal design. The data collected refer to a specific point in time. Changes that might occur over time could, therefore, not be observed. To compensate for this, patients with different ages were involved in the study. Furthermore, the patients interviewed were ‘outside’ the disease; only one patient was in an acute phase during their interview. The participants might have described the disease and its impact differently if they were in acute phases of the disease. Although purposive sampling strategies were used, most participants were well educated, married and employed. Many participants were members of the patient organization that distributed the invitation to take part in the study, which entails the risk that these participants were reluctant to say anything that could be perceived negatively by the organization.

The limitations of the systematic review of reasons are the use of only two databases and the languages English and German. Other databases and languages might provide further results. Furthermore, the definition of the key terms, the search for the relevant publications and the

inclusion of the reasons are interpretative and, thus, subjective processes. However, the decisions were made transparent, intersubjectively and are reported according to the relevant guidelines.

CONCLUSION

The current PhD thesis provides empirical and conceptual findings on the ethical and social issues in the context of HCP. Because of the diverse nature of HCP, a broad range of ethical and social issues has been revealed. Concerning the chronic but unstable character of the disease, pathologization has emerged as a specific ethical aspect in the context of the disease. Concerning the hereditary dimension of the disease, ethical issues of genetic testing in familial contexts, such as the sharing of information, have been identified. The study raises awareness of these issues and their interplay, which is important to understanding the complex situation of those affected and providing them individualised optimal care.

The thesis highlights that individuals with rare, genetically determined, chronic conditions, such as HCP, are not abstract individuals but part of many relations. To understand living with HCP in a comprehensive way, it is important to consider not only the individual patient, but also others affected by the disease and their relationships, for example, in the context of families or patient groups. Since these relationships shape living with such a disease and vice versa, the responsibility for managing a disease such as HCP is shared and not only shouldered on the individual patient. Consequently, it is important for healthcare professionals to know the complex situations and to locate the respective relations in the management of genetically determined and chronic conditions. The results of the current thesis build a comprehensive starting point for practitioners managing chronic diseases that are unstable in their nature, but more research is needed to bring the results of this thesis into practice.

The current PhD thesis focuses on HCP, but further research could examine whether the results could be applied to other diseases with the ‘three-sided’ relation of rarity, inheritance and chronicity. More qualitative research is needed, which covers these dimensions and their interplay, to further unravel the complex situations of patients and their families. In particular, long-term studies and comparisons with other patient groups could supplement the information on living with such diseases. In addition, it would be helpful to investigate the roles and responsibilities of groups other than PAOs, such as large civil societies, in order to meet the needs of those affected and their diverse relations in dealing with their diseases.

SUMMARY

Background: To deliver appropriate support to patients and their families, it is central to know the needs of those affected by a disease. As a chronic disease, HCP usually accompanies those affected for their lifetime and can lead to substantial psychological and social consequences for the individuals affected and their families. Since the subjective experience of individuals living with HCP has not yet been investigated, the current PhD thesis examines the ethical and social issues which arise in the context of HCP.

Methods: To get a comprehensive overview of the ethical and social issues involved, different methods were combined. A qualitative study with patients and their relatives was conducted to acquire an understanding of living with HCP. Based on the issues identified, ethical and conceptual analyses and a systematic review were conducted to supplement the empirical findings.

Results: Twenty-four individual interviews and one focus group were conducted. The participants described HCP as a continuous but unstable part of their lives. The 'shifting perspectives model' by Paterson covers this experience adequately, but due to the shifting character of HCP, the participants reported pathologization as a problematical issue in their lives. Additionally, the study demonstrates that genetic testing has a wide influence in familial contexts and is accompanied by normative issues, e.g. related to reproductive decisions. The study revealed the broad range of ethical and social issues that those affected by HCP face. In this context, PAOs are seen as an important source of support by patients and their families.

Discussion: Given the various tasks ascribed to PAOs, it is unclear what roles PAOs have and what responsibilities they bear. Although the conceptual analysis and the systematic review provided an orientation about PAOs' responsibility, no general answer can be given. Instead, each PAO and its specific situation must be evaluated individually. Responsibility as a relational concept can help to structure these situations and to understand the role of PAOs in the healthcare sector and in current bioethical debates better.

Conclusion: The thesis provides empirical and conceptual findings on the ethical and social issues in the context of a rare, genetically determined, chronic disease. It is important to recognize these three dimensions and their interplay to deliver optimal care to those affected. The results build a comprehensive starting point for healthcare professionals managing genetically determined, chronic diseases, but more research is needed to bring the results of this thesis into practice.

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SUPPLEMENTS

Supplement 1: Announcement (interview study).

Supplement 2: Announcement (focus groups).

Supplement 3: Information sheet (interview study/patient version).

Supplement 4: Information sheet (focus groups).

Supplement 5: Informed consent (interview study/patient version).

Supplement 6: Informed consent (focus groups).

Supplement 7: Ethics committee approval (interview study).

Supplement 8: Ethics committee approval (focus groups).

Supplement 9: COREQ checklist.

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Supplement 11: Interview guide (focus groups).

Supplement 12: PRISMA statement.

Supplement 13: List of publications included in the review.

Supplement 14: Publications pertaining to the thesis.

Supplement 1: Announcement (interview study)

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Datum: 19.05.2017

StudienteilnehmerInnen gesucht

Sehr geehrte Damen und Herren,

wir führen eine wissenschaftliche Befragung zur 'chronischen, erblich bedingten Pankreatitis durch und möchten Sie einladen, die Studie durch Ihre Teilnahme zu unterstützen.

Wer wird gesucht? PatientInnen mit erblich bedingter chronischer Pankreatitis sowie deren enge Verwandte (z.B. Lebens-/EhepartnerInnen). Alter der TeilnehmerInnen über 18 Jahre.

Worum geht es in der Studie? Mit der Studie wollen wir herausfinden, was es bedeutet, mit chronischer Pankreatitis zu leben. Ziel der Studie ist, die individuelle Situation der Betroffenen abzubilden und Erfahrungen mit genetischen Testungen, aber auch Erlebnisse mit Forschungsstudien und Patientenorganisationen abzufragen.

Studienablauf: Wir würden mit Ihnen gerne ein Gespräch (Forschungsinterview) führen, in dem wir Fragen zu den oben genannten Themen stellen. Das Gespräch wird ca. 45-60 Minuten dauern und durch ein Mitglied des Forschungsteams bei Ihnen zuhause, in unserem Institut oder ggf. auch telefonisch durchgeführt. Sie haben dabei die Gelegenheit, frei zu erzählen, was Ihnen zu den genannten Themen wichtig ist.

Wir würden uns freuen, wenn Sie diese Studie unterstützen möchten. Die Kontaktaufnahme kann sowohl telefonisch als auch postalisch oder per Email erfolgen.

Für Rückfragen stehen wir Ihnen gerne zur Verfügung.

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Supplement 2: Announcement (focus groups)

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Datum: 22.06.2018

StudienteilnehmerInnen gesucht

Sehr geehrte Damen und Herren,

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Wer wird gesucht? PatientInnen mit erblich bedingter chronischer Pankreatitis sowie deren enge Verwandte (z.B. Lebens-/EhepartnerInnen). Alter der TeilnehmerInnen: mindestens 18 Jahre.

Worum geht es in der Studie? Mit der Studie wollen wir herausfinden, was es bedeutet, mit chronischer Pankreatitis zu leben. Ziel der Studie ist, die individuelle Situation der Betroffenen abzubilden und Erfahrungen mit genetischen Testungen, aber auch Erlebnisse mit Forschungsstudien und Patientenorganisationen abzufragen.

Studienablauf: Wir würden mit Ihnen gerne ein Gruppen-Interview führen, in dem wir Fragen zu den oben genannten Themen stellen. Das Gespräch wird durch ein Mitglied des Forschungsteams auf dem Patiententag des Kongresses „Viszeralmedizin 2018“ am 15. September 2018 in München durchgeführt. Pro Gruppe planen wir 5-7 TeilnehmerInnen. Sie haben innerhalb des Gruppengespräches die Gelegenheit, frei zu erzählen, was Ihnen zu den genannten Themen wichtig ist. Eine genauere Aufklärung zur Studienteilnahme erfolgt, wenn Sie uns Interesse an der Teilnahme signalisieren.

Wir würden uns freuen, wenn Sie diese Studie unterstützen möchten. Bitte melden Sie sich in diesem Fall per Email, telefonisch oder postalisch unter den unten genannten Kontaktdaten

Für Rückfragen stehen wir Ihnen gerne zur Verfügung.

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Supplement 3: Information sheet (interview study/patient version)

Studie "Ethische Aspekte bei hereditärer chronischer Pankreatitis: Eine qualitative Interviewstudie" im Rahmen von PePPP
("Proteinfehlfaltung, ER-Stress und Proteindegradation – Entwicklung einer systematischen Pipeline für individualisierte Therapien bei erblichen Leber- und Pankreaserkrankungen")

Teilnehmerinformation (PatientIn)

Sehr geehrte Damen und Herren,

wir führen eine wissenschaftliche Befragung zur 'erblich bedingten chronischen Pankreatitis durch. Wir bitten Sie, die Studie durch Ihre Teilnahme zu unterstützen.

Worum geht es in der Studie? Mit der Studie wollen wir herausfinden, wie Ihr Leben mit dieser Krankheit ist. Dazu bitten wir Sie, uns in einem 45-minütigen Gespräch (Forschungsinterview), Fragen zu diesem Thema zu beantworten. Wir interessieren uns in diesem Zusammenhang auch für Ihre Erfahrungen mit genetischen Testungen und Ihre Erlebnisse mit Studien und Patientenorganisationen.

Studienablauf: Das Gespräch wird durch ein Mitglied des Forschungsteams bei Ihnen zuhause, in unserem Institut oder ggf. auch telefonisch durchgeführt. Für Ihre Teilnahme an dieser Studie wurde keine Versicherung (z. Bsp. für Wegstrecken) abgeschlossen. Sie haben im Gespräch die Gelegenheit, frei zu erzählen, was Ihnen zu den oben genannten Themen wichtig ist. Das Gespräch wird aufgezeichnet und später verschriftlicht. Das Forscherteam wertet dann Ihr Gespräch zusammen mit anderen Gesprächen aus und präsentiert die Ergebnisse in Zeitschriften, Büchern oder auf Konferenzen. Bei diesen Präsentationen der Ergebnisse ist kein Rückschluss mehr auf Sie als Person sowie auf andere Personen und Orte möglich.

Freiwilligkeit: Selbstverständlich ist die Teilnahme an unserer Studie freiwillig. Ihre Daten werden nur dann verwendet, wenn Sie die dem Fragebogen beigefügte Einverständniserklärung unterschreiben. Wenn Sie nicht teilnehmen möchten, müssen Sie nichts unternehmen. Außerdem können Sie jederzeit, auch bei bereits erteilter Einwilligung und ohne Angabe von Gründen, aus der Studie ausscheiden. Entscheiden Sie sich gegen eine Teilnahme, hat dies keinerlei Nachteile für Sie. Mit der Einwilligung zum Gespräch würden Sie uns aber sehr helfen, die Studie erfolgreich durchzuführen.

Datenschutz: Alle von Ihnen im Gespräch gemachten Angaben sind nur den Mitgliedern des Forschungsteams zugänglich. Eine Weitergabe Ihrer persönlichen Angaben an Dritte wird nicht erfolgen. Die von Ihnen im Gespräch gemachten Angaben werden in pseudonymisierter Form (d.h. ohne Namen) mit Hilfe eines Computers ausgewertet. Einzelne Zitate können in wissenschaftlichen Artikeln oder Vorträgen verwendet werden, ohne dass eine Zuordnung zu Ihrer Person möglich ist. Nach Abschluss der Untersuchung werden Ihre persönlichen Daten vollständig gelöscht.

Bitte bewahren Sie diese Teilnehmerinformation auf, damit Sie jederzeit nachlesen können, worin Sie eingewilligt haben.

Wir bedanken uns herzlich für Ihre Unterstützung unserer Forschung!

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Supplement 4: Information sheet (focus groups)

Studie „Ethische Aspekte bei hereditärer chronischer Pankreatitis: Fokusgruppen“ im Rahmen von PePPP („Proteinfehlfaltung, ER-Stress und Proteindegradation – Entwicklung einer systematischen Pipeline für individualisierte Therapien bei erblichen Leber- und Pankreaserkrankungen“)

Teilnehmerinformation (Angehörige und PatientInnen)

Sehr geehrte Damen und Herren,

wir führen eine wissenschaftliche Befragung zur ’erblich bedingten chronischen Pankreatitis durch. Wir bitten Sie, die Studie durch Ihre Teilnahme zu unterstützen.

Worum geht es in der Studie? Mit der Studie wollen wir herausfinden, wie das Leben mit dieser Krankheit ist. Wir interessieren uns auch für Ihre Meinung zu genetischen Testungen. Nicht nur die Perspektiven der PatientInnen, sondern auch die Sichtweisen der nahen Angehörigen interessieren uns dabei. Deshalb bitten wir Sie, in einem Gruppengespräch über diese Themen mit anderen InterviewteilnehmerInnen zu diskutieren.

Studienablauf: Zwischen fünf und sieben TeilnehmerInnen sollen an dem Gespräch teilnehmen. Das Gruppengespräch wird ungefähr eine Stunde dauern und durch ein Mitglied des Forschungsteams geleitet. Für Ihre Teilnahme an dieser Studie wurde keine Versicherung (z. Bsp. für Wegstrecken) abgeschlossen. Sie haben im Gespräch die Gelegenheit, frei zu erzählen, was Ihnen zu den oben genannten Themen wichtig ist. Das Gespräch wird aufgezeichnet, protokolliert und später verschriftlicht. Das Forscherteam wertet das Gruppengespräch zusammen mit anderen bereits geführten Interviews aus und präsentiert die Ergebnisse in Zeitschriften, Büchern oder auf Konferenzen. Bei diesen Präsentationen der Ergebnisse ist kein Rückschluss mehr auf Sie als Person sowie auf andere Personen und Orte möglich.

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Supplement 5: Informed consent (interview study/patient version)

Studie „Ethische Aspekte bei hereditärer chronischer Pankreatitis: Eine qualitative Interviewstudie“ im Rahmen von PePPP
(„Proteinfehlfaltung, ER-Stress und Proteindegradation – Entwicklung einer systematischen Pipeline für individualisierte Therapien bei erblichen Leber- und Pankreaserkrankungen“)

Einverständniserklärung

Ich habe die Teilnehmerinformation gelesen und bin über Zweck und Inhalt der Studie informiert worden.

Mir wurde versichert, dass keine personenbezogenen Angaben (wie z.B. Name, Geburtsdatum) oder sonstige Angaben, die Rückschlüsse auf meine Person zulassen, an Dritte weitergegeben werden. Die in der Untersuchung erhobenen persönlichen Daten werden pseudonymisiert und gelöscht, sobald sie für die weitere wissenschaftliche Auswertung nicht mehr benötigt werden.

Ich weiß, dass die Teilnahme an der Befragung **freiwillig** ist. Mir ist erklärt worden, dass meine Entscheidung gegen eine Teilnahme an der Studie keine Nachteile für mich haben wird. Mir ist bekannt, dass ich meine Einwilligung **jederzeit**, ohne Angabe von Gründen, zurückziehen kann. Von mir bis dahin erhobene Daten werden in diesem Falle gelöscht.

☐ **Ich bin damit einverstanden, dass enge Angehörige von mir (Lebens-, EhepartnerInnen, Eltern oder Kinder) ebenfalls an der Studie teilnehmen und befragt werden.**

Hiermit erkläre ich mich bereit, an der Studie teilzunehmen:

_____ _____

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Universitätsmedizin GREIFSWALD

Supplement 6: Informed consent (focus groups)

Studie „Ethische Aspekte bei hereditärer chronischer Pankreatitis: Fokusgruppen“ im Rahmen von PePPP („Proteinfehlfaltung, ER-Stress und Proteindegradation – Entwicklung einer systematischen Pipeline für individualisierte Therapien bei erblichen Leber- und Pankreaserkrankungen“)

Einverständniserklärung

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Supplement 7: Ethics committee approval (interview study)

EINGANG 07. JUNI 2017

Universitätsmedizin
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Ethikkommission

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BEARBEITER
Frau Dr. K. Saljé

Studientitel:	Ethische Aspekte bei hereditärer chronischer Pankreatitis: Eine qualitative Interviewstudie
Antrag vom:	18.05.2017
Eingegangen am:	19.05.2017
Interne Reg.Nr.:	BB 074/17

DATUM
02.06.2017

Stellungnahme der Ethikkommission

Sehr geehrte Frau Prof. Salloch,

die Ethikkommission der Universitätsmedizin Greifswald hat die zum o.g. Versuchsplan eingereichten Unterlagen in ihrer Sitzung am 30.05.2017 geprüft.

Die Kommission stellte mehrheitlich fest, dass gegen die Durchführung der Studie keine ethischen und rechtlichen Bedenken bestehen, und befürwortet deshalb das Vorhaben.

Die Ethikkommission erlaubt sich aber folgende Hinweise.

- Die Archivierung der digitalen Aufzeichnungen der geführten Interviews sollte unter Einhaltung entsprechender Sicherheitsstandards erfolgen.
- Es sollte auch die Einwilligung der Patienten zum Interview der engen Angehörigen eingeholt werden.
- In der Einwilligungserklärung sollte klargestellt werden, dass eine pseudonymisierte Speicherung der erhobenen Daten erfolgt.

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USt ID:
DE137584813

Die Ethik-Kommission macht darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens beim Studienleiter und allen beteiligten Ärzten liegt. Zusammensetzung und Arbeitsweise entsprechen den gesetzlichen Bestimmungen. Den Beratungen der Kommission liegt die Deklaration von Helsinki in der aktuellen Fassung zugrunde.

Die Mitglieder der Kommission wünschen Ihnen viel Erfolg bei der Durchführung des Vorhabens.

Mit freundlichen Grüßen

Prof. Dr. Th. Kohlmann
Vorsitzender der Ethikkommission

UNIVERSITÄTSMEDIZIN GREIFSWALD · KÖRPERSCHAFT DES ÖFFENTLICHEN RECHTS
VORSTAND: Prof. Max P. Baur (Vorstandsvorsitzender) Prof. Dr. Claus-Dieter Heidecke (komm.) Marie le Claire
AUFSICHTSRATSVORSITZENDER: Sebastian Schröder
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Zur Bewertung haben der Kommission vorgelegen:

- Begleitschreiben vom 18.05.2017
- Studienprotokoll, Version vom 18.05.2017
- Leitfaden Patient, undatiert
- Leitfaden Angehörige, undatiert
- Sozialdemographie Patient, undatiert
- Sozialdemographie Angehörige, undatiert
- Patienteninformation, undatiert
- Angehörigeninformation, undatiert Einwilligungserklärung, undatiert

Der Ethikkommission gehören an:

reguläre Mitglieder	*ständige Stellvertreter*
Prof. Dr. M. Lerch* Klinik für Innere Medizin A	*Prof. Dr. S. Stracke* *Klinik für Innere Medizin A*
Prof. Dr. B. Kordaß* Zentrum für Zahn-, Mund- und Kieferheilkunde	*Prof. Dr. R. Biffar* *Zentrum für Zahn-, Mund- und Kieferheilkunde*
Prof. Dr. B. Rauch* Klinik und Poliklinik für Neurologie	*OA Dr. F. von Podewils** *Klinik und Poliklinik für Neurologie*
OA Dr. M. Gründling* Klinik für Anästhesiologie und Intensivmedizin	*OÄ Dr. S. Friesecke* *Klinik für Innere Medizin B*
Prof. Dr. J. Kühn Institut für Diagnostische Radiologie und Neuroradiologie	*Dr. Dr. G. Engel* *Universitätsapotheke*
Prof. Dr. Th. Kohlmann* Institut für Community Medicine	*Prof. Dr. W. Hoffmann* *Institut für Community Medicine*
Prof. Dr. B. Bockholdt Institut für Rechtsmedizin	*Prof. Dr. S. Salloch* *Institut für Ethik und Geschichte der Medizin*
Prof. Dr. H.-W. Eckert* Fakultät für Rechts- und Staatswissenschaft	*Prof. Dr. H. Lang und Prof. Dr. C. D. Classen* *Fakultät für Rechts- und Staatswissenschaft*
Prof. Dr. H. Assel Theologische Fakultät	*Prof. Dr. M. Werner* *Institut für Philosophie*
PD Dr. S. Schmidt* Klinik und Poliklinik für Kindermedizin	*PD Dr. R. Bruns* *Klinik und Poliklinik für Kindermedizin*
CA Dr. Frank Ruhland* Fachabteilung für Gynäkologie und Geburtshilfe, HELIOS Hanseklinikum Stralsund	*OÄ Dr. K. Belau* *Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe*
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Lars Kaltheuner, Medizinstudent	*Katrin Packhäuser, Medizinstudentin**

*bei der Sitzung am 30.05.2017 anwesend

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Supplement 8: Ethics committee approval (focus groups)

EINGANG 8. MAI 2018

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Ethikkommission

GESCHÄFTSSTELLE
Universitätsmedizin Greifswald
Ethikkommission
Institut für Pharmakologie
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BEARBEITER
Frau Dr. K. Saljé

Studientitel:	Ethische Aspekte bei hereditärer chronischer Pankreatitis: Fokusgruppen
Antrag vom:	09.04.2018
Eingegangen am:	11.04.2018
Interne Reg.Nr.:	BB 053/18

DATUM
30.04.2018

Stellungnahme der Ethikkommission

Sehr geehrte Frau Prof. Salloch,

die Ethikkommission der Universitätsmedizin Greifswald hat die zum o.g. Versuchsplan eingereichten Unterlagen in ihrer Sitzung am 24.04.2018 geprüft.

Die Kommission stellte mehrheitlich fest, dass gegen die Durchführung der Studie keine ethischen und rechtlichen Bedenken bestehen, und befürwortet deshalb das Vorhaben.

Die Ethik-Kommission macht darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens beim Studienleiter und allen beteiligten Ärzten liegt. Zusammensetzung und Arbeitsweise entsprechen den gesetzlichen Bestimmungen. Den Beratungen der Kommission liegt die Deklaration von Helsinki in der aktuellen Fassung zugrunde.

Die Mitglieder der Kommission wünschen Ihnen viel Erfolg bei der Durchführung des Vorhabens.

Mit freundlichen Grüßen

A. Be

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Konto-Nr. 130 015 30
BLZ 130 000 00

USt ID:
DE137584813

Zur Bewertung haben der Kommission vorgelegen:

- Begleitschreiben vom 09.04.2018
- Studienprotokoll, Version vom 06.04.2018
- Teilnehmerinformation (Angehörige und PatientInnen) und Einverständniserklärung, Version vom 06.04.2018
- Fragebogen Sozialdemographie - PePP-Fokusgruppen, Version vom 06.04.2018
- Interviewleitfaden, Version vom 06.04.2018

Der Ethikkommission gehören an:

reguläre Mitglieder	*ständige Stellvertreter*
Prof. Dr. M. M. Lerch Klinik für Innere Medizin A	*Prof. Dr. S. Stracke** *Klinik für Innere Medizin A*
Prof. Dr. B. Kordaß* Zentrum für Zahn-, Mund- und Kieferheilkunde	*Prof. Dr. R. Biffar* *Zentrum für Zahn-, Mund- und Kieferheilkunde*
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Katrin Packhäuser, Medizinstudentin*	*Annika Eikenbusch, Medizinstudentin*

*bei der Sitzung am 24.04.2018 anwesend
#nicht an der Beschlussfassung beteiligt

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Supplement 9: COREQ checklist

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Topic	Item	Guide questions/description	Reported on Page
Domain 1: Research team and reflexivity			
Personal Characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	15
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	15
Occupation	3	What was their occupation at the time of the study?	15
Gender	4	Was the researcher male or female?	15
Experience and training	5	What experience or training did the researcher have?	15
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	13
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	Not reported
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	Not reported
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	15-16
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	13-14
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	13
Sample size	12	How many participants were in the study?	21
Non-participation	13	How many people refused to participate or dropped out? Reasons?	21
Setting			
Setting of data collection	14	Where was the data collected? e.*g. home, clinic, workplace*	21
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	Not reported
Description of sample	16	What are the important characteristics of the sample? *e.g. demographic data, date*	21-22; Table 3
Data collection			

Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	14; Suppl. 10 and 11
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	Not reported
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	15
Field notes	20	Were field notes made during and/or after the interview or focus group?	15
Duration	21	What was the duration of the interviews or focus group?	21
Data saturation	22	Was data saturation discussed?	Not reported
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	Not reported
Domain 3: Analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	Not reported
Description of the coding tree	25	Did authors provide a description of the coding tree?	Table 2 (examples)
Derivation of themes	26	Were themes identified in advance or derived from the data?	16
Software	27	What software, if applicable, was used to manage the data?	16
Participant checking	28	Did participants provide feedback on the findings?	Not reported
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	22-29
Data and findings consistent	30	Was there consistency between the data presented and the findings?	22-29
Clarity of major themes	31	Were major themes clearly presented in the findings?	22-29
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	Not reported

From: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007. Volume 19, Number 6: pp. 349 – 357.

Supplement 10: Interview guide (interview study/patient version)

Interview guide 'Ethical aspects in the context of hereditary chronic pancreatitis – a qualitative interview study' (patient version)

START/INTRODUCTION	
Dear [...], I am glad that you are available for an interview with me.	Introduction
Before we begin, I would like to say a few words about the course of the interview. I would like to record the interview so that I could focus more on talking with you. Do you agree?	Recorder
[If the participant agrees, switch on the recorder. If the participant does not agree, take notes.]	
The recorder is running now. We have already talked about the voluntariness of your participation in this research project. Please feel free to interrupt or to end the interview at any time you want. Otherwise, you can talk as much as you like – I have time.	Voluntariness Interruptions Encouragement
Do you have any questions about the interview?	Questions
Today, I would like us to talk about your disease, hereditary chronic pancreatitis.	
How did you realize that you have this disease?	Start

THEME I: PATIENT BIOGRAPHY	
The diagnosis is often a long process. Would you tell me something about it?	Way to diagnosis
How did you realize you were ill?	
How/when did you hear that you have pancreatitis?	
Has something changed since the diagnosis?	
What happened after diagnosis?	
What is it like to live with the disease? (Changes between 'normal' and 'acute' illness phases?)	Living with the disease
How are you doing with the disease right now?	
Do you have any restrictions in your daily life?	Education

Does the disease affect your education/job?	School / Job
Does the disease affect your family life?	Family life
Would you complete the following sentence for me:	
Living with chronic pancreatitis means for me ...	

THEME II: GENETIC TESTING	
We have already talked about the long way to diagnosis. Today, it's also possible to carry out a genetic test. Have you done such a test?	Motivation
Yes/No: Can you tell me, why did you decide in this way?	Decision making process
Would you describe for me which aspects influenced your decision?	
Can you pretend to be in this situation again? How was that? Would you decide differently today?	
Was there any consultation? If so, how did you feel about it?	Consultation
Did you include other people in the decision-making?	Family
If participant did the test:	
What did you do with the information?	Dealing with the information
Did you share the information with other people? If so, how did they react?	
Has something changed in your life because of the information?	Influence of information
Did the information affect something? Can you give me an example?	
So far, we have talked a lot about chronic pancreatitis; does the topic 'cancer' also play a role in your life?	
What do you think of when I bring up the topic 'cancer'?	Cancer
How do you deal with this issue?	

THEME III: PATIENT GROUPS	
We have contacted you about the association […]. Can you tell me how you came into contact with this group? / Why did you become a member of this group?	Reasons
Would you tell me what this group does?	

What are you talking about in the group? Does the group also invite external people?	Functions
How do you help each other?	Role
Is there anything else you want to tell about the group?	
Can you describe an example of how you get support from the group?	Support
Are you missing something?	
As a patient, do you want more support, for example, from your doctor?	

THEME IV: RESEARCH PARTICIPATION	
As a last point, I would like to talk to you about the topic 'biomedical research.'	Experience
Have you ever participated in a clinical study?	
Yes: Can you tell me how it came about? Why did you participate in the study?	Motivation
(What kind of study? What did you do? Do you know the results of the study?)	
No: Two possibilities: Patient has not yet had the opportunity to participate in a study or patient has decided against participation.	Reasons against
Imagine that biomedical research had enough money and all the technical instruments to explore anything you wanted. Regarding chronic pancreatitis, what would you like explored?	Wishes

OPEN ENDED
Do you want to tell me something that we have forgotten to speak about in the interview?
Is there anything else you want to add?
Social demographics
Finally, I have only a few more specific questions…
Thank you very much!

Reprint in slightly modified form by Mueller et al. 2021b.

Supplement 11: Interview guide (focus groups)

Interview guide: 'Ethical aspects in the context of hereditary chronic pancreatitis – focus group'

START	
INTRODUCTION OF THE MODERATOR, THE ASSISTANCE AND THEIR TASKS **EXPRESSING THANKS** **INFORMATION ABOUT THE STUDY**	My role is that of a moderator: I will ask you some questions and control a little bit the discussion. However, you can talk freely to each other. My assistance keeps an eye on the time and writes a small protocol. I am glad that you participate in this focus group session. Some of you know our study already, but not everyone knows what our project is about. In our study we want to investigate how it is to live with Hereditary Chronic Pancreatitis (HCP). We are interested in your experience with research, genetic testing and patient self-help groups. To obtain the views of patients and relatives on these topics, we have already conducted interviews. Today, we want to complement these interviews with a group discussion and I am looking forward to discuss the topics with you.
RECORDER	Before we begin, I would like to say a few words about the course of the discussion. I would like to record the discussion so that I could focus more on talking with you. Do you all agree? [If the participants agree, switch on the recorder. If the participants do not agree, take notes.] The recorder is running now.
VOLUNTARINESS **INTERRUPTIONS** **ENCOURAGEMENT** **CONFIDENTIALITY**	We have already talked about the voluntariness of your participation in this research project. Please feel free to interrupt or to end the group session at any time you want. Otherwise, you can talk as much as you like – We have time. Please keep the statements that will be made within this group to you. This is important to build a trustful atmosphere for the discussion. If there is anything that you do not want to say in front of the group, you can write it down and tell me later, for example after the group session. As I have already explained, I have the role of a moderator. But, I will lead the conversation just a little bit; you can talk freely to each other.

QUESTIONS	There is only one rule: Please do not interrupt each other. Otherwise, you can talk as much and freely as you like. Are there any questions about the discussion?
INTRODUCTION OF THE PARTICIPANTS	Some of you already know each other. Nevertheless, I would like to ask you to write down your names on the cards, introduce yourself in one or two sentences and explain why you are taking part in this patient day for HCP.

FAMILY LIFE	
FAMILY LIFE **INPUT: QUOTES CONSEQUENCES OF HCP**	I'd like to start with the topic of 'family life', because we found very different formulations in the interviews. I brought you two quotes as examples. One participant told us: 'The family comes close because of the disease.' But another participant said: 'The family broke because of the disease.' You can take one of the cards and say something about it, if you want. Can you understand one or both of these formulations?

FAMILY PLANNING	
FAMILY PLANNING **DECISION FOR OR AGAINST CHILDREN** **REASONS** **DECIDING UNDER UNCERTAINTY** **FEELINGS OF GUILT**	I would like to discuss another point with you about 'family life'. Some participants in the interviews told us that the genetic character of HCP had an influence on their decision for or against children. I know this is a very difficult topic. Just say something about it, if you want. Would you tell me your experience / your thoughts? Is there anything else you want to tell about this topic? In this context, one participant said: 'It's like Russian roulette.' Can you explain that to me? Another participant told us: '[...] you're blaming yourself as a mother. You sit there and think, God, I just want the best for my kid, and you give her an illness like that. What kind of mother am I?' Can you understand that? How do you deal with this issue?

GENETIC TESTING WITHIN THE FAMILY	
GENETIC TESTING	As patients you have already undergone various tests. Today it is possible to do genetic testing for HCP. Is genetic testing different from other tests, such as a blood test, in your view? Would you tell me what the difference is?
COUNSELLING	Did you have any counselling before or after the testing? How did you feel about the counselling?
TESTING WITH THE FAMILY TOGETHER	Some participants told us in the interviews that the genetic test was underwent by the family together. How was it in your case? How do you feel about it?
INPUT: ROLE CARDS **WHO SHOULD DECIDE?**	Hand out the cards (doctor, patient, partner, children, parents, friend and plain cards). Who should participate in the decision for or against testing and why? Would you like to say something about these roles?
TIME OF TESTING **INPUT: TIMELINE**	We have already talked about who should decide or be involved in the decision-making process, but when do you think is the right time for genetic testing? You can take a pen, put a cross on the timeline and say something about it, if you want.
TESTING IN CHILDHOOD	Some participants in the interviews reported genetic testing in childhood. What do you think about that?

OPEN ENDED	
OPEN QUESTION	Do you want to tell something that we have forgotten to speak about it in the group? Is there anything else you want to add?
SOCIAL DEMOGRAPHICS	Finally, I have only a few more specific questions… Thank you very much!

Reprint in slightly modified form by Mueller et al. 2021b.

Supplement 12: PRISMA statement

Section/topic		Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	18
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Not applicable
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	18
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	PICOS does not apply but objectives are specified on page 18
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No registry available for this type of review
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	18
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	18
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	19
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	19
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	19

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Not reported
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable (see limitations for explanation)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	20 Figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Not applicable
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	31-32
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g.,	31-32

		healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	37
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	36
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page of the thesis

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Supplement 13: List of publications included in the review

List of all 97 included publications in the systematic review of reasons.

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Supplement 14: Publications pertaining to the thesis

Mueller R, Aghdassi AA, Kruse J, Lerch MM, Rach C, Simon P, Salloch S. Lived experience of hereditary chronic pancreatitis - a qualitative interview study. Chronic Illn. 2021 Sep 24:17423953211039774. doi: 10.1177/17423953211039774.

Original Research Article

chronic illness

Chronic Illness
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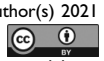
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Lived Experience of Hereditary Chronic Pancreatitis – A Qualitative Interview Study

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Abstract

Objectives: Hereditary chronic pancreatitis is a rare condition characterized by intermittent acute episodes of pancreatitis and long-term impairment of pancreatic functions. However, the subjective perspective of individuals affected by hereditary chronic pancreatitis has been little studied. This qualitative study investigates the experience of hereditary chronic pancreatitis patients and their relatives because the awareness of the needs of those affected is an essential component of a patient-centered management of chronic conditions.

Methods: Semi-structured qualitative interviews were conducted with hereditary chronic pancreatitis patients and their relatives. Data were analysed using qualitative content analysis. The concepts of 'biographical contingency,' 'biographical disruption' and the 'shifting perspectives model' served as theoretical frameworks.

Results: A total of 24 participants (17 patients, 7 relatives) were interviewed individually. Four main themes were identified: (1) The unpredictable clinical course of hereditary chronic pancreatitis; (2) hereditary chronic pancreatitis as a devastating experience; (3) hereditary chronic pancreatitis as part of a normal life; and (4) being reduced to hereditary chronic pancreatitis.

Discussion: The 'shifting perspectives model' of chronic illness covers the four dimensions adequately and can serve as a theoretical model to explain hereditary chronic pancreatitis patients' experience. A better understanding of the patients and their families' experience and the shifting

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character of hereditary chronic pancreatitis can help healthcare professionals to tailor the care to meet the needs of those affected.

Keywords
Chronic illness, hereditary chronic pancreatitis, biographical disruption, 'shifting perspectives model', bioethics

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Introduction

As a basic prerequisite for effective chronic illness care, healthcare systems have to meet the needs of those who are affected.[1] Frameworks for managing and improving chronic care processes, such as the Chronic Care Model (CCM) and its adaptation for international contexts, the Innovative Care for Chronic Conditions framework, have recommended care consistent with the patients' preferences for more than two decades.[1,2] According to the CCM, effective chronic illness care is, among others, based on the individualization of care according to patients' needs and values.[1] The implementation of the CCM can improve medical outcomes and enhance the health-related quality of life of patients with chronic illness, yet, there are some limitations of the CCM and knowledge gaps regarding the benefits and barriers during CCM implementation in different healthcare settings.[3] Although the CCM has been criticized in different aspects, for example, its lack of attention to chronic multimorbidity[4] and paediatric populations,[5] and consequently expanded, for example in the Patient-Centered Medical Home Model,[6,7] 'the model still holds.'[8]

Its core components, emphasizing the individual needs and preferences of those affected and their self-management support, are still relevant subjects of current research on chronic conditions, for example, the barriers and facilitators to self-management in chronic illness[9] or the potential improvements for patients through self-management support.[10] The subjective perceptions of patients with chronic illness have become a relevant part of this research focusing, for example, on the quality of chronic illness care,[11] the factors affecting self-management[9] and the support of self-management.[12] However, although the perspectives of patients and their needs have received increasing attention in both chronic illness care and research, many rare chronic conditions, such as hereditary chronic pancreatitis (HCP) and the specific needs associated, are still underexposed in research.

The current paper presents findings on the subjective experience of patients with HCP and their relatives as part of a larger research project on hereditary disorders of the pancreas and liver [http://www.medizin.uni-greifswald.de/peppp/index.php?id=522&L=1]. The study design has an explorative qualitative character because HCP patients and their relatives have received little systematic empirical scrutiny so far. The aim is to acquire a firsthand understanding of those living with HCP. The main research question is, therefore, how do the individuals affected (patients, partners and family members) experience HCP. The concepts of 'biographical contingency' and 'biographical disruption' and the 'shifting perspectives model' serve as theoretical frameworks.

Hereditary chronic pancreatitis

Hereditary chronic pancreatitis (HCP) is a chronically progressive, rare variant of early-onset pancreatitis. Recurrent acute episodes of pancreatitis are accompanied by a persistent impairment of the exocrine and endocrine pancreatic function[13] due to the loss of parenchymal tissue and the

formation of fibrosis.[14] The clinical symptoms can include abdominal pain, nausea and vomiting. Long-term complications are maldigestion and weight loss due to exocrine insufficiency, pancreoprive diabetes, that results from an impairment of endocrine function, and an increased risk of pancreatic cancer.[15,16] Other common complications are pseudocyst formation,[17] bile and pancreatic duct,[18] as well as duodenal obstruction.[19] Since there is no curative treatment for HCP currently, the therapy covers pain management, therapy for endocrine and exocrine insufficiency, and endoscopic or surgical treatment for bile or pancreatic duct stenosis or for the drainage of pancreatic pseudocysts.[19,20] Diagnosis, prognosis and treatment are challenging, as the course of the disease ranges from asymptomatic to very severe forms.[21]

The variations in the clinical course of chronic (and acute) pancreatitis and their adverse impact on health-related quality of life, daily activities and social life have been investigated in a few qualitative studies.[22–24] A recent phenomenological study, describing the patients' perceptions of recovering from an acute pancreatic attack, emphasized the physical and emotional burdens, such as uncertainty and anxiety, in the context of an acute attack.[23] Similar to acute attacks, the chronic form of pancreatitis is associated with psychological burdens for the patients affected.[25] A qualitative study with chronic pancreatitis (CP) patients highlighted the permanent experience of suffering and disruption at the physiological and psychological levels.[22] However, the uncertainties and worries surrounding the acute attacks affect not only the patients but also their relatives.[24] Family members additionally describe the experience of seeing relatives affected by the hereditary form of pancreatitis as a disturbing experience.[26]

Although there is a considerable amount of qualitative research on acute[23] and chronic pancreatitis,[22] there has been far less qualitative research on patients' experience with the hereditary variant of the disease. The concurrence of the dimensions *rare*, *hereditary* and *chronic* may lead to specific challenges for patients and their families, so that the existing research on acute and chronic pancreatitis and, accordingly, the therapy options and support available may not be directly transferable to HCP. Instead, the existing research needs to be expanded to give healthcare professionals a comprehensive picture of what needs to be done when they care for both patients with HCP and their relatives.

Theoretical framework

The subjective experience of living with a chronic condition has received increasing research interest both in medicine and the sociology of health and illness since the 1980s.[27–35] Ongoing debates on chronic illness focus on individual coping strategies,[35] self-management,[36,37] the consequences of a chronic illness for the identity of patients, especially of young patients,[38–40] and the correlations to employment,[41] family[42,43] and social life.[44]

The concept of biographical disruption, according to Bury,[45] often serves as a theoretical background for research on the subjective experience of chronic conditions. Bury conceptualizes chronic illness as a particular type of disruptive experience and argues that the onset of a chronic illness represents a biographical disruption, marking a life before and after illness.[45] The concept of biographical disruption has been paradigmatic in the field of chronic illness studies for a few decades. The more recent literature, however, highlights its limitations and the need for more differentiated concepts, such as biographical reinforcement,[46] biographical flow,[47] recurrent biographical disruption[48] or biographical contingency.[49] The latter approach, for example, conceptualizes chronic illness as an 'only sometimes problem'[49] and describes living with a chronic illness to a large extent as normal and, simultaneously, attributes a disruptive potential to the illness.[49]

Although the research has become increasingly differentiated, many approaches have in

common that they understand chronic conditions as predictable linear paths.[50] However, the idea that a person with a chronic illness follows a trajectory is, in Paterson's opinion, misguiding and incomplete.[50] Her 'shifting perspectives model' of chronic illness describes living with a chronic condition as an ongoing, continually changing process in which either elements of illness or wellness can be in the foreground.[50] The perspective of the patient can shift from illness (i.e. illness dominates the daily life) to wellness (i.e. illness is largely unnoticed) and *vice versa*, for example, because the subjective illness experience or the social context changes.[50] Due to the variation in the clinical course of HCP known from the literature, Paterson's account seems to be a suitable lens for the current study because of the possibility of variation and individualization of the illness experience.

Methods

Study design

The lack of research on the subjective experience of HCP in the literature influenced the development of the study aim and research question. Due to the gap, the aim of the present study is to acquire a firsthand understanding of those living with HCP. The main research question is, therefore, how do the individuals affected (patients, partners and family members) experience HCP? An exploratory qualitative design was chosen to clarify the relatively unknown experience of living with HCP.[51] Qualitative semi-structured interviews were used because they allow one to elicit data grounded in the participants' experience, while they retain some relation to the theories identified in the literature, namely, the concept of biographical disruption and the shifting perspectives model of chronic illness.

The development of the interview questions was carried out in a stepwise process. In the first step, based on the existing literature and the research team's experience, brainstorming was conducted to collect possible questions. In addition to the main research question of how those affected experience HCP, the theories identified in the literature led to further questions. The concept of biographical disruption, for example, which focuses on the onset of a chronic illness, raised questions about the diagnosis of HCP; the shifting perspectives model of chronic illness led to questions on the changes between 'normal' and 'acute' illness phases. In the second step, all questions collected were checked for their suitability, e.g. whether the questions were relevant to the objectives of the study. In the last step, the relevant questions were sorted and grouped into themes, e.g. in 'changes of illness phases.' The resulting interview guide starts with theoretically driven open-ended questions about the diagnosis of HCP, through questions about living with HCP to those about the changing illness phases, and ends with a more narrative question about the meaning of living with HCP for the person affected (Box 1).

Box 1. Interview questions (selection/version for patients).

How did you realize that you have this disease?

The diagnosis is often a long process. Would you tell me something about it?

How did you realize you were ill?

How/when did you hear that you have pancreatitis?

Has something changed since the diagnosis?

What happened after diagnosis?

What is it like to live with the disease?

Changes between 'normal' and 'acute' illness phases?

How are you doing with the disease right now?

Do you have any restrictions in your daily life?

Does the disease affect your education/job?

Does the disease affect your family life?

Would you complete the following sentence for me: Living with chronic pancreatitis means for me …

Two slightly modified versions of the interview guide, one for patients and one for relatives, were developed. One interview with a patient and one with a relative as face-to-face pilots were conducted by RM, a female PhD student. These two interviews were included in the final analysis as the pilot test resulted only in minor modifications to the interview guides.

Study participants

Both patients and their relatives were invited to participate in the current study since the family context has been proven to be a major factor in the context of chronic conditions.[24,26,42,43] A patient organization for patients with HCP and their families in Germany (Deutsche Pankreashilfe e.V.) was involved to gain access to potential study participants. This organization has had a longstanding close relationship with two of the researchers (MML and PS). The chairperson of the organization forwarded an open invitation to participate in the interview study to the members by email and verbally at events arranged by the organization. Individuals who responded to these calls received written information about the context and objectives of the study by email and post. RM contacted those interested by telephone to clarify any remaining questions. Snowballing sampling was additionally used to locate further study participants, for example, individuals who are not members of the patient organization: Those contacted through the patient organization were asked whether they could forward the open invitation to others who could be interested in becoming study participants.

The sample was restricted to patients who self-identified as HCP patients, i.e. patients who had a personal history of pancreatitis and/or had been tested for the hereditary form (PRSS1 mutations) and/or already had HCP in their family ($\geq$2 individuals with pancreatitis in $\geq$2 generations). Although HCP could not be verified in every patient by previous genetic test results, it was assumed because of the personal history of pancreatitis, the occurrence of HCP in the family and the absence of other explanatory etiologies (e.g. alcohol). Inclusion criteria regarding unaffected family members restricted the sample to the parents, children, siblings, aunts, uncles, spouses and life partners of HCP patients. The inclusion criterion, at least 18 years of age, applied to all participants. Variations in age, gender, educational level, marital status and the course of the disease were aimed for in the sampling.

Data collection and analysis

The individual face-to-face interviews were conducted by RM (trained in empirical bioethics and qualitative research) at the participant's home. If a personal visit was difficult for the interview participant to arrange, telephone interviews were offered as a backup option. The same interview guide was used in the telephone interviews as in the face-to-face interviews, but the participants were contacted by telephone prior to the actual telephone interview to build trust and rapport and enable a free-flowing conversation. In order to gain the participant's full attention during the telephone interview, instructions were given in advance to provide enough time and a quiet room without potential disturbances.

All interviews (both the face-to-face and the telephone interviews) were fully audio-recorded, transcribed verbatim and pseudonymized. In addition to the audio recording, the interviewer made field notes during and after all interviews.

The interview transcripts were analysed using content-analytical procedures. The methodology selected for the data analysis was qualitative content analysis according to Mayring.[52] Qualitative content analysis is a systematic data analysis technique. It was selected as the analytic method because it is independent of theoretical perspectives, very flexible and provides a systematic way of reducing and synthesizing a wide range of data.[53] Its

Table 1. Themes and categories with examples.

Themes	Categories	Sub-categories	Representative quotes
Unpredictable clinical course of HCP	HCP as an ongoing but unstable condition	Episodic occurrence; disappearance; comparison with a cycle	*Yes, it does restrict me, but not as much as another illness that I would have all the time. Because in my case it only occurs in episodes and then it usually goes away again.(Interview 5)*
Unpredictable clinical course of HCP	Unpredictability; not knowing; fear of attacks; helplessness	Unpredictable clinical course; Russian roulette; disease not known; always expecting an attack; reason for the attack unknown; at the mercy of the disease	*Especially in the beginning, the first few years, it was unpredictable and because I didn't know what I had, it was like a game of roulette or Russian roulette for me, where I always had to expect that I would be lying down the next day and that I wouldn't know why and was at the mercy of it. (Interview 11)*
HCP as a devastating experience	Restrictions	Restrictions in general; effects in many areas; not being able to do things as wanted	*Well, for me, it means restrictions in many areas, you can't do the things the way you want but, on the other hand, it's also a disease that you can definitely live with. (Interview 15)*

central idea is to assign categories to text passages through a qualitative-interpretative act.[52] The analysis follows a systematic procedure and strict content-analytical rules combining deductive and inductive category development.[52]

Correspondingly, the transcripts were worked through with a previously developed, deductively formulated category system derived from theory. RM and SS categorized the interview text into clusters of conceptual categories with the aid of the deductively formulated category system and the software program MAXQDA12. Additionally, new categories were formulated out of the text. A coding scheme was created using the deductive and inductive category development and deliberated in recurring team meetings (for examples of the themes and (sub-)categories, see Table 1). Finally, the coding scheme was applied to all transcripts and the results were further interpreted regarding the categories generated. The team discussions and the different professional backgrounds of the researchers (medicine, philosophy and ethics) are intended to mitigate the rater influence.

The present study is reported according to the COREQ checklist for qualitative research (Supplement 1) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants and they were informed that study participation was voluntary. Other research ethics requirements, such as data protection, were followed diligently. The institutional Ethics Committee of the University Medicine Greifswald approved the study (ref. BB 074/17).

Results

Twenty-six participants were enrolled in the interview study between July 2017 and December 2019. Two participants declined to be interviewed for personal reasons, resulting in a total of 24 individual interviews. Of these 24 interviews, 17 were with patients and 7 with relatives. Twenty-two participants were interviewed in their own homes; two interviews were conducted by telephone. The interviews lasted an average of 44 minutes (median: 43 minutes), ranging from 16 to 91 minutes.

Table 2. Sample characteristics.

Characteristics	Patients (n = 17)	Relatives (n = 7)	All (n = 24)
Age	20–70 (median: 49)	47–78 (median: 67)	20–78 (median: 52.5)
Age groups			
18–30	2		2
30–50	7	1	8
50–70	7	5	12
70–90	1	1	2
Gender			
Male	7	3	10
Female	10	4	14
Genetically tested	11		11
In acute episode	1		1
Education			
A-level	10	2	12
Secondary school	5	2	7
Other	2	3	5
Marital status			
Single	5		5
Married	11	7	18
Living together	1		1
Has children	12	7	19
Employment	13	5	18
Member of patient organization	11	3	14
Relationship to patient			
Parent		3	3
Spouse		4	4

Reprinted: Müller et al.[64].

Different stages of HCP were covered in the study. The patients had had a clinically overt condition since their birth, childhood or adulthood and one patient was in an acute phase of the condition during the interview process. In order to cope with complex familial relationships during the interview study, participants were asked to assign a role to themselves, which resulted in the three categories: Patient, partner and parent. Most participants were married, well-educated and more than 30 years old. Most of the participants had children and worked at the time of the interview study. Further characteristics of the interview participants can be seen in Table 2. Since HCP patients and their relatives are a relatively small group in Germany, characteristics such as the role of the interview participant, their gender and age are not indicated in the following quotes to guarantee anonymity. More information about the study results is available from the first author upon request.

Four topics were chosen as the focus of the current paper due to the richness of the results: (1) The unpredictable clinical course of HCP; (2) HCP as a devastating experience; (3) HCP as part of a normal life; and (4) being reduced to HCP.

The unpredictable clinical course of HCP

The study revealed that those affected by HCP experienced the illness as an ongoing but unstable and unpredictable condition. The participants described that the acute phases of the illness always return, likening it to a cycle. They emphasized, additionally, that the course of the illness could not be predicted. The participants could not say when and how long the acute phases would last. Phases of one to several days were reported. Some participants experienced several phases in short intervals, others no acute phases for many years. The participants reported uncertainty and feelings of powerlessness regarding the acute phases because they could not say what caused an impending exacerbation. In addition, from their perspective, nothing could be done in advance against becoming symptomatic

again. Since they could influence neither the occurrence nor the course of the acute phases, both patients and family members felt helpless and at the mercy of the illness.

> You just got over it, and then it started again. [Interview 15]

> We live on a powder keg. We don't know when it will come because it is so, well, unpredictable. It can go bad; it can go well for a long time. [Interview 17]

Some participants said that they were always vigilant of new episodes. They highlighted that they always had to be prepared for potential acute phases. One participant reported, for example, that the laundry was constantly done so that everything was ready should an acute phase of the illness come. Relatives particularly referred to an increased attention and alertness in their daily lives. One relative, for example, reported phases in his/her family life, in which he/she continuously paid attention to the noises at night to hear if there might be something wrong with the family member affected, even if he/she was not in an acute phase of the illness.

> Well, a certain fear is stored somewhere inside yourself that now, suddenly, a phase will come, and you would be at the mercy of it again. Yes, you're always a little bit on guard. [Interview 11]

The participants also indicated various restrictions and turning points in their lives due to the unpredictable character of the illness, for example, in terms of education, job fulfilment or family planning. Other aspects of life in which the participants felt restricted by the unstable course of the illness extended to vacation plans, going abroad, sports, leisure and social activities. The participants reported that they had had to cancel their plans or appointments due to acute phases and that it was difficult to plan anything at all.

> At the beginning, I dare not go anywhere. Now, I can't go on holiday with my grandchildren alone because if I had such a phase somewhere […] it would be a shock for them [the grandchildren]. [Interview 3]

> At university, I had been promised that I could go to the USA, but due to the illness, which occurred for the second or third time, there were problems with the health insurance […] that was also a limitation, which hurt me very much. [Interview 4]

HCP as a devastating experience

The acute phases were described very differently by the participants, ranging from mild to very severe. The severe phases were usually described as lasting a few days, but one participant also spoke of several weeks. Again, the participants could not say with certainty what had triggered an acute exacerbation. In the case of the latter, the participants reported that they were extremely weak. They described, for example, a rapid loss of physical energy and feelings of being ineffective and impassive. Furthermore, they could no longer eat and drink and, in the worst case, had had to go to the hospital. The description often focused on extreme pain, which could not be treated but was actually unbearable. The pain and weakness particularly brought them to their physical and psychical limits.

The participants who had experienced a severe phase designated it as a disruptive experience. They described it as devastating, very frightening and reported fear of death as an example. Furthermore, they emphasized that the severe phases took them out of their everyday life, for example, from work, that they had no longer been able to do anything and that the severe phases are very difficult to endure.

> This [the acute phase] is really a point where you think, well, it can't go on. […] and you can't really go back into life because you always have some pain and so on and you don't know

what's going on now. That worries you. [Interview15]

Family members expressed similar feelings regarding severe phases. When acute phases occurred, relatives were very concerned about the patient's well-being and afraid that the phases could worsen. Some reported concern about repeated visits to the hospital and physicians; others stated the fear of the patient's death. Relatives who had observed the patient's suffering reported that the severe phases would be extremely difficult to bear for them.

HCP as part of a normal life

The participants also experienced long episodes in which the illness remained unremarkable and unnoticed. Some participants reported no acute phases for several years or even decades. The participants emphasized that the illness disappeared after acute phases and explained that their lives were then comparable to those of healthy people. Several participants did not label themselves or their relatives as being ill but, on the contrary, as being healthy. Parents particularly did not want to talk about their children as being ill.

But as soon as I'm out of the hospital and go back into everyday life and realize, ah, everything is fine and everything is the same as with everyone else, then it's hard for me to say, yes, I have an illness, because it's not present at that moment. [Interview 5]

In addition, the participants regarded HCP as an inevitable part of their existence, as a part that has always been part of their lives because nothing could be done about it. Some participants saw HCP as an essential component, which had made them the person they are today. In several interviews, the participants relativized restrictions and difficulties, which they had mentioned previously. Comparisons to other conditions, such as cancer, were often used to relativize HCP and the associated burdens.

On the other hand, our neighbor has pancreatic cancer now. By comparison, I'm fine at my age. Or when I was in rehab and saw the problems of others, I told myself, I have nothing bad at all. [Interview 3]

Being reduced to HCP

Some participants criticized that others tended to reduce those affected to their illness and the associated aspects. They experienced that other people only noticed the disease and not the person or the current context of the person's state of health and illness. One participant reported, for example, that once he/she had mentioned the disease, the conversation partner only wanted to talk about HCP, although the participant him/herself would have preferred to talk about other topics. Another example was the participants' experience in healthcare, particularly during medical examinations. They reported that other health issues had been overlooked by the medical staff as they focused exclusively on the pre-diagnosed HCP.

[…] and you're often reduced to the disease […] this is often worse for me than anything else. So, this is sometimes forgotten a bit, that you can be a normal person in addition to the disease and still have other problems […]. So, if I just go to a doctor now and say I have the disease, then he just looks at me at this point and at nothing else. I always say, yes, but I also have other things. That is, I think, very, very important. [Interview 5]

In this context, the participants spoke about expectations regarding the patients' behaviour, which often came with the attribution of illness. Some participants had experienced, for example, that others expected them to eat healthily, not to drink alcohol, smoke or do risky sports. One participant, for instance,

stated that in his/her childhood he/she had been excluded from sport because of HCP, even though he/she would have been able to attend sports classes.

Discussion

The results present four categories describing the subjective experience of those living with HCP and show particularly the unpredictable dimension of living with the illness. The findings show that HCP is an illness with a very unstable character whose manifestation can range from mild to very harmful experiences. Although their interview study focuses on acute pancreatitis, the results of Boije et al.[23] confirm the wide variation of the intensity and duration of acute pancreatic phases. Furthermore, the participants described feelings of uncertainty, anxiety and fear due to the lack of knowledge regarding why and at what time the pancreatic attack had occurred.[23] In a previous survey by Shelton et al.[24] participants with hereditary pancreatitis (HP) expressed similar feelings, describing the worry and uncertainty about when an acute phase will occur. Moreover, feelings of helplessness were described by both the patients regarding their own disease and relatives observing the patients' suffering.[24] The participants in the present study confirmed these findings by reporting fear, uncertainty and helplessness due to the unplannable and sudden experiences of the acute phases.

The impact on health-related quality of life, for example, regarding daily activities and psychosocial well-being, described in the survey by Shelton et al.[24] were echoed in the current study, demonstrating restrictions regarding social activities, education and job fulfilment. Related findings have been described in the interview study by Boje et al.[23] indicating that the physical suffering of pancreatic attacks has adverse effects on every day and social life. A recent qualitative study with CP patients by Cronin and Begley[22] highlights the permanent experience of disruption at the physiological, social and psychological level. By contrast, participants in the current study depicted phases of exacerbation but, in between, the disease was predominantly invisible.

In the current study, both patients and family members have described the acute severe phases as a devastating experience. This disturbing dimension of the illness can be found in other studies. Although in the context of genetic testing of HP, both a survey by Applebaum-Shapiro et al.[26] and the one by Shelton et al.[24] refer, for example, to the 'disturbing nature of seeing relatives affected with HP.' At first glance, the description of the devastating experience by the participants in the present study is reminiscent of Bury's concept of biographical disruption.[45] According to Bury, the onset of a chronic illness separates the patient's life into a lifespan before and after illness. In the study with CP patients by Cronin and Begley, the participants described such a shift from a well person to a person with CP.[22] The unplanned and sudden transformation from being healthy to being in an acute phase were also described in the study with patients with acute pancreatitis by Boije et al.[23]

However, the participants in the current study did not report such a clear transition. They spoke instead of recurring disruptive moments as part of their ongoing biography. The disruptive dimension of HCP refers neither to the participants' entire biographies, nor to a single point in their lives, but rather to the recurring difficulty of integrating the acute illness phases into daily life. The concept of biographical disruption by Bury, thus, cannot completely mirror the viewpoints of individuals affected by HCP. These findings are in accordance with several studies which show that the concept of biographical disruption is only relevant to the experience of chronic illness to some extent.[46–49,54]

Most participants in the current study had grown up with the diagnosis of HCP and/or were already familiar with the illness because of its occurrence in the family. However, even if familiar with or expected, the acute phases could be disruptive. The

unpredictability of the phases was, besides their strength, an important reason for this. Patients with acute pancreatitis similarly described the burden of the unplanned and sudden occurrence of the acute phases, which includes shocking and unreal sensations.[23] The experience of HCP patients is, thus, in accordance with the concept of biographical contingency.[49] This concept describes life with a chronic illness as normal, which means undisturbed, to a large extent. Since the chronic illness is only experienced from time to time, the biographies and the daily routines are disrupted only momentarily.[49] By describing life with a chronic illness as normal and, at the same time, granting the disease a disruptive potential, the concept of biographical contingency covers the dimensions expressed by the study participants adequately.[49]

Altogether, the study reveals that HCP can be understood neither as a linear predictable path nor as a dichotomy of life before and after illness but as a continuous, constantly shifting process. This description is covered by Paterson's 'shifting perspectives model' of chronic illness.[50] As described in the current interview study, the perspectives of the participants can shift in the model from illness (i.e. an acute phase is in the foreground) to wellness (i.e. HCP is largely unnoticed) and *vice versa*.[50] Paterson's model helps to resolve the seemingly contradictory statements of the participants. Several participants, for example, stated that living with HCP was never normal because they always had to be vigilant about acute phases. At the same time, the participants said that the disease had disappeared after the acute phases and then they led a normal life. In addition, the illness in itself and the associated difficulties were often relativized throughout the interviews. Paterson's model can cover these variations in the participants' attention to HCP and meets the individual character of the illness experience.

The ethical problem of being reduced to HCP is linked with the shifting process. The changing character of HCP can lead to diverging perceptions. Because the illness is not always present, participants describe themselves as healthy, whereas others label them as ill. This misattribution can be seen as a form of pathologization.[55–57] The experience of being reduced to the illness and labelled as ill is described by the study participants as problematic because the attribution often leads to expectations regarding the participants' behaviour and can even pave the way for a depersonalization or objectification of the participants. A reductive view can lead to severe problems for the individual in the healthcare system, for example, when other diseases or symptoms are overlooked. In addition, conflicts can arise if the perceptions of those affected and healthcare professionals diverge and patients or their relatives do not behave as expected by the healthcare professionals.[58] The experience of being reduced to the illness could be prevented in the context of the healthcare system by focusing on the patient and his/her interests rather than the disease. The exchange with other affected patients and family members could provide further assistance, especially in dealing with feelings of helplessness, being at the mercy of the illness and reduced to it. Consequently, a next step could be to develop a program of psychological support for HCP patients and their families and to provide more support for different forms of patient self-help.

A further step to develop better care and support for those living with HCP could be to ensure long and constant but, at the same time, phase-specific support. Trustful collaborations between patients, families and healthcare professionals are essential for high-quality care, especially in the context of long-lasting chronic conditions.[58,59] A better understanding of the shifting character of HCP and the associated problems can help healthcare professionals to establish a trustful relationship and provide sustainable support. In addition to trustful and permanent support, specific assistance in the respective phases is very important. Consequently, it should be ensured that the

knowledge of the changing character of HCP is integrated into the scientific and practical education of healthcare professionals.

Strengths and limitations

The current study was designed to elicit a deeper understanding of living with HCP and, as far as the authors are aware, it is the only study of this kind. One strength of this study is the use of semi-structured interviews because they allowed more in-depth information and provided detailed insights into how those affected experience HCP. Another strength is the inclusion of both patients and their relatives. Partners and family members often added further information to the findings. Maximum variation sampling was used to ensure the inclusion of participants of differing gender, in different parts of their lifespans and with varying levels of HCP. HCP is a rare disease. The prevalence of the disease and the difficulty in diagnosing and recruiting HCP patients and their families for a research study, therefore, limits the sample size of this study. The participants were contacted via a patient organization, thus, it is possible that the participants were reluctant to make comments that might be perceived as critical about the support of the organization. The recruitment via the patient organization also resulted in a slight majority of patient organization members among the individuals interviewed. Individuals with HCP who were not members of the organization were much more difficult to contact by the research team and, therefore, represent a smaller proportion in the sample. The membership of an organization could indicate a more 'engaged' cohort.

It was not possible for two participants to conduct the interviews at home. These interviews were, therefore, conducted by telephone. There are differences in the data collection between face-to-face interviews and interviews by telephone and an important and unresolved issue about social desirability bias generated through telephone interviews.[60] The nuances of body language, for example, and other non-verbal cues associated with face-to-face interaction may be lost over the telephone, and trust is difficult to establish.[60]

Furthermore, the participants' medical conditions might have had an influence on the study results. Only one of the participants interviewed was in an acute episode at the time of data collection. Talking from a place 'outside their disease,' the participants might have reported other aspects than they would have had in an acute phase. Finally, the study does not have a longitudinal design but instead reproduces the participants' views at a particular point in their lifespan. Longitudinal qualitative research with repeated interviews throughout could provide further information on the subjective experience of HCP. The analysis of qualitative data is not a straightforward process, often accompanied by concerns, e.g. on reliability and generalizability, and there are different opinions about which criteria are the best for evaluating the trustworthiness of qualitative content analysis.[61–63] Concerns related to trustworthiness are minimized in the current study by several strategies, such as protocolling the different stages of the analysis, regular reflective discussions within the research team and full reporting of the process of data analysis. In addition, researchers with different disciplinary backgrounds were part of the study team to mitigate assumptions and bias during data analysis.

Conclusion

The current paper presents findings on the subjective experience of patients with HCP and their relatives showing implications resulting from HCP as a chronic but constantly changing condition. A better understanding of the unpredictable and shifting character can help healthcare professionals to tailor the care to meet the needs of those affected. Individual support for HCP patients should be patient-focused, cover psychological support and be carried by both the healthcare system and the social network, for example, patient self-help groups. Further

research should investigate what specific forms of support HCP patients and their families need and how the different forms of support can help in the acute phases, affect the phases between the acute attacks, and help to deal with the problem of pathologization. The focus of the current study is on the experiences of HCP, but the issues discussed are potentially relevant to other chronic conditions that are variable in their nature. Further research should address how the unpredictable and constantly changing character of chronic conditions can be better considered in the research and development of therapies and the scientific and practical training of healthcare professionals.

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Supplement 1: COREQ Checklist

Trial registration

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Guarantor

RM

Contributorship

RM, SS, SP and MML conceived the study. MML, PS and RM were involved in patient recruitment. RM conducted the interviews. RM and SS conducted the data analysis. RM, SS, CR and JK interpreted and discussed the data. RM wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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ARTICLE

Perceptions of genetic testing in patients with hereditary chronic pancreatitis and their families: a qualitative triangulation

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Abstract

Hereditary chronic pancreatitis (HCP) is a genetically determined condition characterized by intermittent acute episodes of pancreatitis and long-term impairment of the exocrine and endocrine pancreatic functions. Genetic test results can have substantial psychological and social consequences for the individuals tested and their families. Nevertheless, little is known so far about the subjective experience of individuals genetically tested for HCP. This qualitative study examines the viewpoints of HCP patients and their relatives in order to identify the psychosocial and ethical implications related to genetic testing within families. Semi-structured qualitative individual interviews and a focus group with HCP patients and their family members were conducted. Data were audio-recorded, transcribed verbatim and analysed using qualitative content analysis. A total of 28 individuals were enrolled in the study: 24 individuals (17 patients, 7 relatives) were interviewed in semi-structured one-on-one interviews and 4 individuals (2 patients, 2 life partners) participated in the focus group. Emerging topics covered (1) genetic testing in childhood, (2) genetic testing within the family and (3) family planning. The study reveals that genetic testing for HCP has a wide influence in familial contexts and is accompanied by normative issues, such as autonomy, reproductive decisions and sharing of information within the family. The results raise the awareness of the complexity of family contexts: familial relationships and dynamics can have great influence on the individual decisions related to genetic testing. Increased understanding of these relational contexts can help health professionals, for example, in counselling, to discuss genetic testing better with patients and families.

Introduction

Hereditary chronic pancreatitis (HCP) is a rare variety of chronic pancreatitis (CP) which is characterized by intermittent acute episodes of pancreatitis and long-term impairment of the exocrine and endocrine pancreatic functions [1] due to loss of parenchymal tissue and formation of fibrosis [2]. The term 'hereditary pancreatitis' is usually reserved for a category of the disease associated with germline mutations in the cationic (PRSS1) trypsinogen gene [3] and distinguished from other varieties, which can also be associated with genetic risk factors but are not inherited in an autosomal dominant manner [4]. The latter are sometimes referred to as familial pancreatitis.

The clinical presentation can include recurrent abdominal pain, nausea and vomiting, maldigestion, pseudocyst formation [5], and bile duct [6] and duodenal obstruction [7]. Currently, there is no causative treatment for HCP and therapy focuses, as in other forms of CP [8], on pain management, therapy for endocrine and exocrine insufficiency, and endoscopic or surgical interventions for complications [9]. The course of the disease varies from asymptomatic to very severe forms [10].

As a rare genetic disorder, HCP is diagnosed predominantly in individuals of European origin [11]. It was first described as a genetically determined disease in 1952

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[12] and later identified to be associated with mutations in the cationic trypsinogen (PRSS1) gene [13]. It required extensive experimental research [14] before it was discovered that the underlying mechanism involves the resistance of the disease-relevant, mutant trypsinogen isoforms against degradation by chymotrypsinogen C [15]. However, despite comprehensive research, many unanswered questions regarding HCP remain and the identification of further mutations and the interplay of genetic, epigenetic and environmental factors are the focus of current studies.

CP, in itself, represents a psychological burden for the patients affected [16]. Suffering from a genetic form of the disease carries an additional dimension for patients and their relatives. Currently, genetic testing by direct DNA sequencing is available for many diseases. It is widely discussed not only in biomedical research but also from sociological, psychological and ethical perspectives [17–20]. The complexities of dealing with genetic test results, consequences of genetic knowledge, impacts on families, discrimination and stigmatization are the focus of the debates [17–20]. Regarding families, topics such as prenatal testing, reproductive decisions, sharing of information within the family and attitudes regarding genetic testing have been discussed [21–25].

The effects of genetic information depend on many factors, such as the condition being tested and the social context of the test [26]. Regarding HCP, genetic testing can lead to early diagnosis and insofar prevent the further search for and misattribution of the underlying cause of the disease. A diagnosis of HCP also provides a causative explanation to patients about the origin of their underlying disease which may facilitate coping with the disease. It can also provide useful prognostic information and options for family planning [27, 28].

The International Association of Pancreatology (IAP) formulated criteria for genetic testing for HCP which refer to the clinical presentation, the family history and the eligibility for study participation (Table 1) [29]. In addition to these indications, the recommendation of the IAP addresses especially the counselling process and privacy issues [29]. Moreover, ethical issues, such as patient autonomy, informed consent, prenatal testing, testing in minors and the impact on family members, are debated in the recommendation of the IAP and in other contributions [20, 27].

Table 1 Criteria for genetic testing for HCP according to the International Association of Pancreatology [ref. 29].

Criteria for genetic testing for HCP
Patients with recurrent attacks of acute pancreatitis without explanation
Patients with idiopathic chronic pancreatitis
Individuals with a family history of pancreatitis in a first- or second-degree relative
Children with an unexplained episode of documented pancreatitis who require hospitalization and where there is significant concern that hereditary pancreatitis should be excluded
Patients with pancreatitis eligible for an ethics committee approved research protocol

However, little is known regarding the impact of such testing on patients and their family's lives. The current study is the first qualitative study focusing on both the viewpoints of HCP patients *and* their relatives on the genetic testing for HCP. The psychosocial and ethical implications associated with HCP genetic testing are discussed not only for the individual but also for the family. The involvement of relatives in the current study can help to reach a comprehensive picture of the effects of genetic testing on family life. The study specifies the experiences with genetic testing regarding HCP but expands, at the same time, the existing research on genetic information within families. In doing so, the study aims to explore the psychosocial and ethical implications of genetic testing for HCP to elucidate the impact of genetic testing for rare chronic diseases in family contexts.

Materials and methods

Qualitative triangulation was used to investigate how genetic testing affects patients and their relatives' lives. Triangulation, as the combination of different approaches to study the same object of inquiry, can refer to such different aspects as data, investigators, theories or methods. Method triangulation can refer to the combination of quantitative methods, qualitative methods or both. Method triangulation in qualitative inquiry means a multimethod approach to qualitative data collection and analysis, which can refer, for example, to the combination of qualitative methods such as one-on-one interviews and focus groups [30]. The underlying idea of all approaches is to study the respective phenomenon from different perspectives in order to gain a more complete picture and deepen the understanding [30]. In the present study, individual interviews were supplemented by a group session to discuss the psychosocial and ethical aspects of genetic testing within families.

As participants can contradict or complement each other in discussions, ethical issues, which are often vague and implicit, can be well crystallized in group sessions. Throughout the discussion, different ethical dimensions of a topic can be collected, which, in turn, can strengthen the findings and enrich the interpretation. Furthermore, the focus group can be seen as a test of validity of the results from the individual interviews. The additional group session can help to reduce biases or deficiencies caused by one-on-one interviews with a

researcher. In the group session, the participants talk among themselves, which can lead to a better integrity and consistency of the research findings.

The interview guide for the individual interviews was developed containing four major topics: patient biography, experience with genetic testing, biomedical research and patient self-help groups. The interview guide was pilot tested. One interview with a patient and one interview with a relative were conducted as pilots face-to-face by RM. As only minimal changes to the interview guide emerged from the pilot testing, these two interviews were included in the final analysis. The interview guide was used for individual interviews with patients and family members (Suppl. 1). Based on the results of the individual interviews, the interview guide for the focus group, targeting the topic of genetic testing within families, was developed (Suppl. 2).

The study was approved by the Ethics Committee of the University Medicine Greifswald. Written informed consent was obtained from all study participants. Research ethics requirements, such as data anonymity, were observed diligently.

Study participants: sampling for individual interviews and focus group

The study sample was drawn from individuals participating in a German self-help organisation for patients with HCP and their families. MML and PS, who have a long-standing contact to the patient organisation, established contact with the chairperson. The latter passed on the request to participate in the study to the members of the organisation. Patients who responded to this call, volunteered to participate in the study and identified themselves as HCP patients. They were sent an e-mail invitation by RM. When the person contacted confirmed his/her interest, written information about the context and goals of the study were sent by post and RM contacted the prospective participants additionally by telephone to resolve potential questions. Participants recruited in this way were asked whether they would forward the invitation to participate in the study to further patients and relatives (snowballing technique).

Inclusion criteria restricted the sample to patients who already had HCP in their families, had been tested for the hereditary form or had thought about a genetic test. Inclusion criteria regarding family members allowed the participation of parents, children, siblings, aunts, uncles, spouses and life partners. All participants had to be at least 18 years old. The participant selection aimed for the greatest possible variation in terms of age, gender, level of education, familial status and disease progression. Sampling was discontinued when data saturation was reached. Data saturation was defined as the point when no new relevant information regarding the aim of the study emerges and the codes become repetitive with only small variations [31].

Data collection

The individual interviews were conducted in a semi-structured style, face-to-face or via the telephone by RM (female PhD student) who has been trained in empirical bioethics and qualitative research. Field notes were made during and after the individual interviews. The interviews were audio-recorded, transcribed verbatim and pseudonymized. In addition, a focus group session with patients and life partners was carried out. Based on the analysis of the individual interviews, the main topic 'genetic testing' was selected for discussion in the focus group. The group session was conducted by the interviewer RM and one assistant. It was audio-recorded, transcribed verbatim and pseudonymized.

Data analysis

The transcripts were analysed by RM and SS using qualitative content analysis according to Mayring to identify codes and categories [32], with the aid of the software program MAXQDA12. The transcripts were encoded, codes and categories were regularly discussed and modified in team meetings, and a coding scheme was developed. The coding scheme was inductively expanded and critically revised. Once theoretical saturation and redundancy had been reached, the results were further interpreted regarding the emerging categories. Rater influence was controlled in team discussions during the coding process and by researchers with different professional backgrounds (medicine, philosophy, and ethics) involved in the data interpretation (Suppl. 3).

Results

The study was conducted between July 2017 and October 2019 in Germany. A total of 28 individuals were enrolled in the study. Two potential participants declined to be interviewed for personal reasons. Twenty-four individuals were interviewed in semi-structured individual interviews (17 patients, 7 relatives) and four individuals (2 patients, 2 life-partners) participated in the focus group.

Potential participants for the focus group were reluctant to discuss the sensitive and private issues of genetic testing in a larger group. Consequently, the focus group session was relatively small consisting of two patients and their partners. The group represented a so-called real group [33], a group that had not been composed specifically for research but existed independently of the research situation.

The participants of the group discussion were already familiar with each other and had had similar experiences because of their involvement in the patient organisation.

Twenty-two of the individual interviews took place at the participants' homes; two interviews were conducted by telephone. The focus group session was held in the context of the annual meeting of the patient organisation. The one-on-one interviews lasted an average of 44 min (median: 43 min), ranging from 16 to 91 min. The focus group took 75 min.

The study included patients in different stages of the disease. The patients had had a clinically overt disease either since their birth, childhood or adulthood. One patient was in an acute phase of the disease during the interview study. Some participants had multiple roles. One participant, for example, was the partner of a patient and, at the same time, the parent of an affected child. As a result of the multiple roles, many different but interwoven familial relationships are covered in the present study. In order to manage this complexity, each participant was formally assigned only one role. The participants themselves chose their roles, which resulted in the three categories: patient, partner and parent. Additional characteristics of the interview participants can be seen in Table 2.

The codes identified from about the 20th interview were not novel in substance but variations on topics which existed already. Four more individual interviews were conducted to make sure that the point of data saturation had been reached. These additional one-on-one interviews confirmed that data saturation had been reached. The focus group was seen as a further validation tool in order to get a robust picture.

Genetic testing in the context of families was identified in the individual interviews as an important but complex issue, associated with different ethical questions. For this reason, the topic of genetic testing was chosen for further discussion in the group session and as a focus of the current paper. Selected study results will be presented in the following with a focus on the impact of genetic testing on patients and their family's lives, particularly regarding (1) genetic testing in childhood, (2) genetic testing undergone by families together, and (3) family planning. Since HCP patients are a relatively small group in Germany, characteristics, such as gender and age are not mentioned in the following quotes in order to guarantee data anonymity.

Table 2 Sample characteristics (individual interviews).

	Patients ($n = 17$)	Relatives ($n = 7$)	Total ($n = 24$)
Age	20–70 (median: 49)	47–78 (median: 67)	20–78 (median: 52,5)
Age groups			
18–30	2		2
30–50	7	1	8
50–70	7	5	12
70–90	1	1	2
Gender			
Male	7	3	10
Female	10	4	14
Education			
A level	10	2	12
Secondary school	5	2	7
Other	2	3	5
Marital status			
Single	5		5
Married	11	7	18
Living together	1		1
Having children	12	7	19
Employment	13	5	18
Member of self-help group	11	3	14
Genetically tested	11		11
In acute episode	1		1
Relationship to patient			
Parent		3	3
Spouse		4	4

Genetic testing in childhood

The study participants debated the topic of genetic testing during childhood, referring to tests in their own childhood and tests for their children. A few participants did not remember whether a test was done during their childhood. Some participants reported that a test had been done, but that they were not informed about the test results. Other participants remembered the testing process but did not remember the test results.

> *Well, I didn't notice that it [genetic testing] was done, […] when I was twelve years old, it was just said, we had this genetic defect. [Interview 18, Patient]*

> *Once [the physician] did a genetic test, but I never got an answer. [Interview 1, Patient]*

Many participants were unsure how they themselves could assess and judge genetic testing in childhood. Regarding the optimal time for testing, for example, testing at different ages and for different reasons were suggested. Participants explained that genetic testing was such a highly individual decision that the right time for testing could not be determined in general. Instead, it depended on when the first symptoms occurred and how the person affected utilized the test results. Although different ages for testing were discussed, many participants named adolescence as an appropriate time for testing. Reasons against earlier testing were that children have had too little life experience and

must first develop the ability to understand and decide about this complex issue. Testing immediately after birth and in early childhood was, therefore, rejected by most of the study participants. On this point, no differences between patients and family members could be observed and consensus was also reached in the focus group. Tests in adolescence were supported by many participants because, in their view, genetic testing could lead to certainty about the disease and its origin and the testing could have a reassuring effect.

I would say, early in [adult] life, because then it brings more certainty that you know where it comes from. [Focus group]

As I said, it's very, very difficult, when you are a kid. As a kid, you are inexperienced anyway. [Focus group]

In addition, the role and responsibility of the parents were addressed by the participants. Some found it essential that the parents know about the genetic status of the disease to be able to react appropriately. By contrast, other participants emphasized that it could have strong negative consequences for the subsequent childhood if parents panic as a reaction to the test results and put their children under strong surveillance.

I think it's also very important […] how the parents react at that moment. Do they panic 'we have to do this and that' or do they deal with it very calmly and sensibly? I think this is very important, even for the rest of your life. It shouldn't be underestimated. Of course, taking precautions, but there are, I say, these 'helicopter parents': 'Rather not, better not, not at all, and no, you aren't allowed to go to friends and eat elsewhere,' although there's nothing yet. [Focus group]

Some patients reported that their parents had been concerned about their further development as a consequence of the test results and that they, therefore, had been taught to be cautious about various aspects of life. Parents had restricted, for example, physical activities, such as sports, leisure activities, such as horse riding, or going abroad. One participant reported that he/she had been excluded from sports classes in his/her childhood due to HCP, although—from his/her own perspective—he/she would have been able to do sports. In this context, the participants also reflected on their own biography with the disease and the complex interaction of disease, environment and their own behaviour.

But I also know that it [the disease] is not the only factor […]. Of course, I don't know, my childhood itself, living with this disease: what made me what I'm today? Not everything can be attributed to the condition, but also the circumstances that I had, how they changed me, my personality, my character. I think it all comes together. [Interview 19, Patient]

Genetic testing within the family

Participants also reported how entire families had undergone genetic testing together, but that the issue had not been discussed previously within the family. Several participants (belonging to one family), for example, described that an appointment had been made for them all to go to the physician together and undergo the test one by one. Some said that the question of whether to undergo the test together had been a simple question of 'yes or no'. Others reported that the question had not been asked at all.

Why should you make huge discussions about this? Either Yes or No. [Interview 10, Relative]

No, this wasn't really discussed much, because it was always clear that I would get maximum support, so to say. So, it was clear, okay, we are here together now, we do this together now. [Focus group]

One motivation for going through the testing process together was wishing to know which family member was the gene variant carrier of the disease. Another reason was the family's wish to support the person affected. In this context, some participants described a certain 'sense of togetherness'. Assuming the test would have little or no negative consequences, many participants did not see any reasons against undergoing testing together as a family. Some participants refused to test together as a family because, in their view, the test would not change anything. In addition, some participants preferred the state of not knowing: 'What I don't know won't hurt me' [Focus group]. Although most participants were interested in their family members' opinions, they also emphasized that the decision for or against testing was up to the patient.

Everyone else is, of course, asked for their opinion, or perhaps simply what they would do, so that I can hear what they have to say. I want to hear what they have to say, but, at the end of the day, I'm the person who makes the decision. [Focus group]

Family planning

The participants described that family planning was an important but difficult issue for them and that genetic aspects mattered. They emphasized the wish to have a healthy child and the concern of passing on the disease.

It definitely makes the decision more difficult because you're worried, because you know what could happen. And that's not very nice and you don't want that for your children. That's clear. This will always be in my mind, for years, of course. [Interview 15, Relative]

Some, especially female, patients reported feelings of fear and guilt of transmitting the disease to their children.

I felt this between my mother and me and I feel this now between me and my daughter. And, you're blaming yourself as a mother. You sit there and think, God, I just want the best for my kid, and you give her an illness like that. What kind of mother am I? […] I certainly felt bad about it, some fear, despair and I think my mother had felt the same. [Interview 11, Patient]

For many participants, the genetic character of the disease was a relevant factor in family planning, particularly in decisions for or against having a child.

[…] then we were told that the chances that our third child […] will also get the disease is 50/50. 'It's your decision' they said. Then we decided, quite deliberatively, not to have a third child. [Interview 17, Patient]

In this context, the theme of abortion was discussed and three reasons against having children were raised: firstly, transmitting the illness is a form of harm and it is not acceptable to harm an innocent person like a child. Secondly, it is not acceptable to pass on the burden of disease to a person who cannot be asked and cannot decide against it. Thirdly, to care for an ill child is too burdensome for the family, especially for the mother.

It's very hard for me to imagine harming someone else […]. A child can't say 'I accept that' and 'that's okay' and all, but instead the child is born, has the genetic defect and must live with it. […] Because of that, I would say, at the moment, I don't want children. [Interview 5, Patient]

Patients and family members reported that the uncertainty whether the disease would be transmitted or not was a burdensome aspect in the decision-making processes for or against having a child. Not knowing whether the child would have the disease led to distress and made the corresponding decision very difficult. In this context, the participants described themselves as powerless.

That's like Russian Roulette. [Interview 22, Patient]

It's not nice, but you have no influence. [Interview 15, Relative]

Some participants stated that they would decide to have children, because they themselves had not experienced the disease as too burdensome and, additionally, that it was not sure whether the child would have the disease. Furthermore, the participants discussed whether it was acceptable to give birth to a child if the expectant mother did not know if she could take care of the child because she did not know how long she would live due to the disease.

It's not just the question, does the child have it [the disease], but am I still there as a parent? […] Maybe it's really a bit selfish to say, yes, I don't care, I'll risk it, even if I'm dead in five years, you [the partner] will have to do it alone then, but, yes, I would risk it. [Focus group]

A few patients indicated that other people, for example, family members, had interfered or tried to influence the decision for or against having children.

My mother said at that time: You have a boy and a girl and if you know that the disease could come with the third child, what more do you want? You have a boy and a girl. Be satisfied. [Interview 17, Patient]

Discussion

Genetic testing during childhood was brought up by the study participants as a major topic and symptoms were seen by the study participants as a major reason for initiating genetic testing. Testing of children who show symptoms has generally been seen as acceptable in literature because it might prevent a long and troublesome period until the correct diagnosis is made. By contrast, predictive genetic testing of children without symptoms is much less acceptable [34–36], particularly regarding incurable diseases, such as hereditary forms of cancer, Alzheimer or Huntington's disease [18, 37–39]. One problem is that predictive genetic testing in childhood deprives the individual of the opportunity to make an autonomous decision as an adult [27, 36]. The 'right not to know' is strongly discussed in this context. Once told, the young person must live with the information about his/her genetic condition. For these (and other) reasons, genetic testing in early childhood is widely rejected [20, 27, 29] which is also mirrored in the present study.

As the discussion in the focus group might suggest, growing up with knowledge about genetic conditions might have effects on the individual's own health, psychological well-being, self-image, and views about parenthood and family. However, recent literature does not confirm the negative psychological effects of predictive genetic testing [26, 36, 38–41].

Predictive genetic testing can result in exaggerated reactions of the parents, as discussed by the focus group participants. Since parents are often concerned about their child's further development when a genetic diagnosis is made, early testing can medicalize childhood and, as also described by the study participants, sometimes lead to excessively cautious behaviour [42, 43]. Parents can see their child as 'at risk' and treat her/him as vulnerable, for example, restricting physical activities, scrutinizing the child's development and overusing the medical system [43]. These concerns described in the literature are consistent with the experience expressed in the present study on HCP. Participants reported, for example, that they had been excluded from sports classes in their childhood due to HCP, although—from their own perspective—they would have been able to do sports. Growing up under observation and restrictions can influence the well-being and development of the child and other family members and shape family life in a negative way [43].

The study participants' argument that there are no reasons for genetic testing in childhood since the test would not change anything is also mirrored in literature regarding other genetic conditions. Professional guidelines on predictive genetic testing of minors usually recommend testing only if effective medical interventions are available to treat, prevent or mitigate the course of a disease [44]. The direct medical benefit to the child is seen as the main justification for predictive genetic testing. If there are no medical consequences, almost all guidelines recommend delaying testing [44]. Since there are, at least currently, no effective interventions or preventive measures for HCP, the IAP also rejects predictive genetic testing for HCP in childhood [29].

As has emerged from the current study, most recommendations suggest delaying testing until the child is old enough to make an informed decision, but there is no consensus about the age at which children can understand the complex issue and give full informed consent [28, 29, 44]. According to the IAP recommendation, a child beyond the age of 12 can begin to contribute to the decision-making process and should, therefore, be included [29]. Many guidelines on predictive genetic testing in minors do not focus on the age itself but instead on the ability of the child to make a free informed decision [44]. The state of development, maturity, competence and understanding are seen as the relevant issues [44]. Participants in the present study named similar conditions to determine the right time for testing. Although different age groups were debated, many participants described adolescence as an appropriate time for testing and rejected testing immediately after birth and in early childhood.

Although professional societies [45] understand genetic testing, in the first place, as an individual and not as a shared choice, participants in the present study described that entire families underwent genetic testing together. Similar to the current study, a previous qualitative study with hereditary pancreatitis patients revealed that the family context plays an important role in decisions regarding genetic testing [46]. Additionally, a systematic review revealed that sharing genetic test results with family members is common [47]. Nevertheless, the review found challenges for the individual in deciding whether to communicate within the family, in assessing what the effects of disclosure could be, in selecting which information to disclose and at what time [47]. Since genetic information does not only affect the individual but also family members, there may be a legitimate interest on the family's side that relatives decide on testing and share their test results. However, familial relationships and associated responsibilities can affect the choice of the individual in such a way that the free individual choice comes into conflict with the family dynamics [48]. The example in the current study of a parent who tried to interfere in their child's family planning illustrates this risk and raises the question whether decision-making processes, which involve family members, are appropriate in the context of genetic testing.

Despite longstanding bioethical debates, no agreement has been reached so far on whether and how family members should become part of healthcare decisions [49].

Careful consideration should, thus, be given in the counselling process to the aspect whether the decision for or against a test is made by the individual alone or together with the family and whether the individual wants to share his/her test results. In Germany, for example, any person who is tested must be given individual genetic counselling by a physician before and after predictive genetic testing [50]. Under certain circumstances, the counsellor may recommend that the relatives of the person tested also undergo genetic testing, but the decision to share this information with the family is entirely up to the person tested. Although the counselling process has to cover psychological and social issues regarding the test and its potential results [50], family issues and dynamics should receive more attention.

Participants in the current study also reported that genetic information has influenced or could influence their reproductive behaviour. The use of a prenatal diagnosis for HCP has not yet been investigated, but it could become an issue in the future with the expansion of prenatal testing. The identification of genetic dispositions in the foetus raises difficult questions, for example, about maintaining a pregnancy or not [42, 43, 51]. Because prenatal testing for HCP cannot predict the onset and severity of the condition, the remaining uncertainties make decisions very challenging and can lead to psychological distress for the parents-to-be [43, 51]. Participants in the present study confirmed these concerns by describing the uncertainty of transmitting the disease as a burdensome and stressful dimension in the decision-making process. In addition to psychological problems, difficulties regarding informed consent arise [43, 51]. The expectant parents need unbiased and evidence-based information and support to clarify their own values [51]. A recent review showed that expectant parents have positive attitudes towards learning about the genetic status of their foetuses and choosing among various prenatal testing opportunities, and that they also manage the process very well [51]. Since participants in the current study and those in other studies reported genetic information as an important factor in family planning, accompanied by uncertainties regarding disease transmission, onset and severity of the condition [42, 43, 51], these aspects should be thoroughly addressed in genetic counselling.

Limitations

Although the current study allows for a deeper understanding of genetic testing in the context of families, the study is subject to the general limitations of qualitative research, such as nonrepresentativeness and subjective interpretations. Since different viewpoints on genetic testing should be covered in the current study, the study also included patients who had decided against genetic testing. Although HCP was therefore not confirmed by genetic testing in every patient, it has been assumed because of both the personal history of pancreatitis and the occurrence of HCP in family members.

Furthermore, the patients' conditions might have had an influence on the study results: only one of the patients interviewed was in an acute episode at the time of data collection. Talking from a place 'outside their disease', the participants might have reported other aspects than in an acute phase. In addition, the study does not have a longitudinal design but, instead, reproduces the participants' views at a particular point in their lifespan. Longitudinal surveys on HCP patients and their relatives may, in addition, provide further relevant information.

Conclusion

The current study is the first qualitative study focusing on the experience with genetic testing of HCP patients and their relatives. The study expands previous research on genetic information and, simultaneously, specifies the experience of genetic testing within the context of HCP. The results raise the awareness of the complexity of family contexts: familial relationships, responsibilities and dynamics can have a great influence on decision-making processes. As no agreement has been reached so far on the issues raised in the current study, for example, the right time for genetic testing in childhood or whether and how family members should become part of healthcare decisions, careful consideration should, therefore, be given to these aspects in the counselling process. Increased understanding of the family context can help health professionals to discuss issues related to genetic testing with patients and families better.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Collective forward-looking responsibility of patient advocacy organizations: conceptual and ethical analysis

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Abstract

Background: Patient advocacy organizations (PAOs) have an increasing influence on health policy and biomedical research, therefore, questions about the specific character of their responsibility arise: Can PAOs bear moral responsibility and, if so, to whom are they responsible, for what and on which normative basis? Although the concept of responsibility in healthcare is strongly discussed, PAOs particularly have rarely been systematically analyzed as morally responsible agents. The aim of the current paper is to analyze the character of PAOs' responsibility to provide guidance to themselves and to other stakeholders in healthcare.

Methods: Responsibility is presented as a concept with four reference points: (1) The subject, (2) the object, (3) the addressee and (4) the underlying normative standard. This four-point relationship is applied to PAOs and the dimensions of collectivity and prospectivity are analyzed in each reference point.

Results: Understood as collectives, PAOs are, in principle, capable of intentionality and able to act and, thus, fulfill one prerequisite for the attribution of moral responsibility. Given their common mission to represent those affected, PAOs can be seen as responsible for patients' representation and advocacy, primarily towards a certain group but secondarily in a broader social context. Various legal and political statements and the bioethical principles of justice, beneficence and empowerment can be used as a normative basis for attributing responsibility to PAOs.

Conclusions: The understanding of responsibility as a four-point relation incorporating collective and forward-looking dimensions helps one to understand the PAOs' roles and responsibilities better. The analysis, thus, provides a basis for the debate about PAOs' contribution and cooperation in the healthcare sector.

Keywords: Patient groups, Collectives, Patient representation, Patient involvement, Bioethics

Background

Patient advocacy organizations (PAOs) have increased in their number and social visibility over the last few decades [1–3]. There are pragmatic reasons for joining forces: Individuals together have more power and better opportunities to advocate for their specific interests than alone. However, there are also moral reasons for joining a PAO, such as helping each other and campaigning for justice. Looking at the common goals and tasks of PAOs, normative values such as justice and ethical motives such as empowerment become apparent. This shows that PAOs are not only active in advocacy, but also cover ethical issues. Moreover, their activities are subject to ethical evaluations and linked with ethical concepts, such as responsibility. The involvement of PAOs in biomedical research [1, 2, 4, 5], politics [6] and industry [7, 8], for example, is seen as controversial and raises questions about the general character of their responsibility.

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Since PAOs are confronted with normative questions of responsibility in these exemplary fields of activity, they are expected to respond. However, it is not always clear for what, to whom and on which basis PAOs are responsible given the complex healthcare systems within which they operate.

The aim of the current paper is to analyze PAOs' moral responsibility to provide guidance not only to themselves but also to political, scientific and industrial stakeholders. Responsibility is presented as a concept with four reference points: (1) The subject, (2) the object, (3) the addressee and (4) the underlying normative standard. This four-point relationship is applied to PAOs and the dimensions of collectivity and prospectivity are analyzed in each reference point.

Patient advocacy organizations

Characteristics and missions

There is a great variety of PAOs [1, 3]. They differ in size, organizational structure, level of professionalization, strategy and financial capacity. There are groups operating at the local level, while others have an international scope. Several groups are working across diseases; other groups are condition-specific [9]. Despite the diversity of the groups, many definitions describe typical attributes for PAOs, such as their nongovernmental, nonprofit and patient-driven character [1, 3, 9, 10]. The PAOs are often defined as "[…] not-for-profit organisations which are patient focused, and where patients and/or carers […] represent a majority of members in governing bodies" [11]. They usually aim at strengthening the voice of affected and sometimes overlooked individuals, and ensure that their interests are recognized [1, 3, 10]. The contribution of PAOs can, therefore, be seen as "[…] representing and voicing the situation of a specific population that would otherwise not be represented" [9]. The groups pursue this mission in various ways. Their activities cover, inter alia, interacting with patients, educational activities [9], promotion of research [2, 10] and engaging in policy and industry [7, 8]. The PAOs often bring together not only those directly affected but also related families, interested individuals, groups concerned with similar problems and professionals.

The shared mission of PAOs to advocate for those affected has its major roots in the experience of injustice, as many PAOs represent, for example, patient groups or diseases that are under-recognized, such as orphan diseases [1, 3]. Consequently, a core normative value that characterizes the work of PAOs is social justice. Moreover, the wish to help each other can be a strong motivator for affected individuals to initiate or join a PAO. Mutual support is, therefore, a further normative value strongly represented by PAOs. In addition, the normative ideal of empowerment can be found in many PAOs, for example, in statements such as 'Strengthening the patient's voice' (for instance: the 'Strengthening Patient Voices project' by the Meningitis Research Foundation). Looking at the core values of the PAOs, the principles of justice, beneficence and empowerment (as one key aspect of autonomy) crystallize. These moral dimensions of the PAOs' work, together with their non-profit and patient-focused character, distinguish PAOs from other organizations in healthcare, such as research institutions, professional bodies or insurances.

In contrast to profit-oriented or politically managed organizations, PAOs can be classified as civil society organizations (CSOs) due to the mentioned dimensions and characteristics. CSOs can generally be defined as non-governmental actors, varying from activists, small community-based groups and informal movements to highly organized institutions and international organizations or networks [12]. One common goal of CSOs is to participate in or influence (health) policy [13, 14] and research [15] on behalf of citizens or socially and economically disadvantaged groups, for example, women, persons with disabilities or migrants [16]. Due to their independence from direct governmental management, their non-economic aims and their voluntary and bottom-up way of working [11], PAOs and CSOs have much in common. However, as CSOs work on a wide-ranging scope of themes, from environment and trade to human rights, PAOs work in the context of healthcare and are motivated by the specific needs and values of patients.

Challenges

The PAOs are confronted with internal and external challenges in their various fields of action and face multifaceted ethical issues. Many activities, for example, confront them with ethical questions regarding representativeness. The criteria which qualify one or more persons to represent a group are not clearly defined and PAOs typically represent various interests simultaneously, for example, of patients and families [17–19]. Additionally, PAOs need to maintain a balance between professionalization and representativeness. More intensive contact with healthcare professionals or companies is often accompanied by less time for the PAO members and eventually can result in a loss of contact with the grassroots [9]. This is accompanied by the risk that the PAOs may decide and act independent of their members and lose sight of their interests. The question of the extent to which individual patients or members can and should participate in the collective decision-making is challenging for each PAO and needs to be addressed at the level of the PAOs' decision-making structures. The distribution of resources,

tasks and responsibilities within PAOs can lead to difficult processes.

Such ethical issues arising *within* a PAO are accompanied by ethical questions occurring *between* different PAOs and other stakeholders. The involvement in politics [6] and research [4, 5] and the cooperation between PAOs and economic stakeholders [7, 8, 20] can sometimes be problematic. Building financial relationships with industrial companies, for example, can help PAOs to pursue their goals [21] but might lead to pressure to conform to the funder's interests [20, 22]. Many organizations have committed themselves to support research. However, PAOs that want to foster biomedical research face many ethical questions, such as the extent to which they should encourage their members to participate in a study or the extent to which the specific interests of the PAO should influence the research designs [4]. Another problem for PAOs can be that external cooperation, for example, with politicians, might be characterized by tokenism [9]. Finally, given the missing access to independent and adequate resources for PAOs [9], questions regarding the fair distribution of resources arise.

These are exemplary challenges showing that PAOs are faced with various ethical questions regarding their internal structures and external activities. Focusing on these ethical issues makes the moral character of PAOs' activities more transparent. When confronted with decisions of ethical significance, justifications of their activities and their implications are required from PAOs: Their actions are then subject to ethical evaluations and linked with the concept of moral responsibility. For example, if a PAO wants to advance biomedical research and is partnering with an economic stakeholder to achieve this goal, this PAO should be able to explicate how many funds the PAO accepts from the economic stakeholder to promote that research. By being able to answer such questions, the PAO demonstrates how it acts in a responsible manner regarding these activities.

Moral responsibility

There are numerous definitions of moral responsibility [23–25], for example, backward- or forward-looking accounts [26] and collective [27–32] or individual approaches [33]. The concept of responsibility in healthcare and medicine has long been discussed [34], for example, different models of responsibility in bioethics [24], the individuals' responsibility for their own health [33, 35, 36], and collective responsibility in healthcare [37–39]. The diversity of literature on responsibility makes it almost impossible even to provide a systematic overview of the main argumentative lines of the discourse. However, responsibility can be generally understood as both a causal and a normative relation [35]. Causal responsibility merely means that somebody (or something) has caused something, whereas the attribution of the consequences remains a descriptive act [23]. In the context of PAOs, the second meaning, responsibility as a normative relation, is of interest. In this meaning, "[…] responsibility refers to the demand on a person or an institution to justify its action or actions towards another person or institution" [35]. The conditions for moral responsibility, for example, free will, are controversial. However, widespread agreement exists on the following key traits: To describe an agent as responsible for an action means that this agent fulfils some epistemic conditions and conditions of control [33]. The agent must have a certain degree of awareness of the consequences of his/her action, including an understanding of their moral significance, and sufficient control over his/her action [33].

Wrongdoings are the typical occasions for asking about responsibility and the respective debates usually refer to the attribution of harm that one individual did to another individual. However, such an individualistic, negative and backward-looking understanding of responsibility does not fully meet the circumstances of PAOs' engagement. Their activities have a collective character, do not usually focus on specific tasks but on a broad thematic issue and their orientation is prospective. Consequently, the dimensions of collectivity and prospectivity could be more appropriate for PAOs' responsibility than the often-used conditions of individuality and retrospectivity.

Collective dimension

Collective responsibility covers situations in which more than one individual can be seen as responsible for something. The responsibility is spread to (members of) a group instead of being bound to one individual [28]. Since many agents in the healthcare system, for example clinics or the medical professions, are groups to which the concept of individual responsibility does not fit, the concept of collective responsibility allows to make sense of collectives in healthcare without having to abandon the notion of individual responsibility. Moreover, modern medical technologies, such as human-machine cooperation, require a reflection on the collective dimension of responsibility in healthcare [40]. If healthcare systems should remain an area in which morality is a relevant factor, a way must be found to make the moral responsibility of these associations understandable. PAOs are only one of several groups that are operating in the healthcare system.

However, since the concept of collective agency and collective responsibility turns groups, as opposed to their individual members, into moral agents, it has been strongly scrutinized both methodologically and normatively in recent years [31]. Despite the comprehensive

research, collective responsibility remains a contentious concept, since it is still unclear whether collectives can become (moral) agents and how collective action and intention are possible at all [27–32, 41–43].

If it is assumed that collectives can bear responsibility, the subsequent question is: how, if at all, can that responsibility be shared within the collective [28]. Some theorists argue that responsibility can only be constructed in individual terms. According to this position, the "responsibility of the group" is merely aggregated individual responsibility and the individuals in the group remain the responsible subjects [28]. The opposite opinion claims, that there is a responsibility of the group on its own and that this responsibility cannot be reduced to the individuals forming the group [28]. Peter A. French, for example, argues that collective responsibility does not entirely consist of or is exhausted by the individuals within the collective [37]. There are not only these binary counterparts, but also other models and many positions in between [39]. The current paper seizes the dispute between these two sides by examining whether a collective dimension is helpful when considering PAOs' responsibility.

Prospective dimension

The classical literature on responsibility usually refers to backward-looking concepts: Much of the literature focuses, for example, on responsibility as guilt [44, 45], accountability [46, 47] and liability [29, 48]. More recent accounts, on the contrary, often draw on forward-looking approaches [49, 50]. Retrospective (or backward-looking) responsibility covers something an agent has done (or omitted to do) and its consequences. It concerns activities in the past. Prospective (or forward-looking) responsibility refers to future activities, often to the occurrence (or prevention) of certain states, and means responsibility for something that is not yet the case [50]. The agent is not obliged to act in a concrete way but to behave in a way that is promoting a certain state. Forward-looking responsibility is often linked with backward-looking responsibility, but the relationship between these two types is controversially discussed [26].

The current paper focuses on the future-oriented dimension because this dimension seems more appropriate for the PAOs' advocacy role and their caring activities. The character of PAOs' goals are usually to change something for a better future, such as improving patient care or raising public awareness of a certain disease. The typical tasks of a PAO, such as policy, education and promoting research and development, are activities aimed at improving the conditions for the individuals affected. As PAOs usually take care of these issues voluntarily and in a patient-driven way, this article sheds light on the caring and future-oriented activities of the PAOs.

Responsibility as a relational concept

As has been mentioned above, in the context of PAOs, the meaning of responsibility as a normative relationship is of interest. Understood as a normative relationship, responsibility manifests in relations between different reference points (relata). Due to various possible relata, the relational understanding is a useful analytical tool to analyze the complex field of PAOs' activities. Although there are concepts using up to six [35] or seven [24] reference points, the following four relata seem—in the view of the authors—at least necessary for moral responsibility: Someone (the subject) is responsible to somebody (the addressee) for something (the object) regarding normative criteria. This four-point relationship will be applied to PAOs, each of the relata will be discussed, and the dimensions of collectivity and prospectivity in each reference point will be analyzed (Table 1).

Table 1 Relata of responsibility in the context of PAOs

Relata of responsibility	Context of PAOs	Dimension of collectivity	Dimension of prospectivity
Subject	PAOs	PAOs as collectivities capable of intentionality, acting and moral responsibility	Long-term structures and far-reaching goals of PAOs
Object	Patient representation and advocacy	Collective representation of a shared interest, respectively, an issue that is important for many people	Campaigning refers to future situations that are not yet the case
Addressee	From a specific (patient) group to others in the health sector and society	Direct benefits to the target group, understood as a collective, and collective, indirect benefits for others	Future patients and generations
Normative standard	Legal regulations; ethical guidelines and codices; ethical principles of justice, beneficence and empowerment	Standards that are the result of a shared deliberative process	Standards that show a certain degree of stability and long-term orientation

Responsibility of PAOs

The subject

The first reference point addresses the subject of responsibility and draws attention to PAOs as collectives and, therefore, to the underlying question whether collectives could be assigned moral responsibility. According to French "[…] something must, at least, be an intentional agent to be properly held morally responsible for its actions" [37]. The debates on responsibility exhibit a close systematic connection between responsibility and intentionality, but also a strong dispute about this relation [46–54]. Following French's argumentation, some collectives are capable of intentionality and can, consequently, bear moral responsibility [37].

French differentiates between aggregate and conglomerate collectivities. A collectivity can be understood as an aggregate "[…] if the identity of that collectivity consists in the sum of the identities of the persons who comprise the membership of the collectivity" [37]. An aggregate is, for example, the people standing on the corner [37]. By contrast, "[…] conglomerates are such that their identities do not entirely consist in or are not exhausted by the identities of the persons that are associated with them" [37]. The conglomerate's identity is insofar independent of its individual members as it is consistent with a (constantly) changing membership. An example is a clinic whose identity remains the same even if all employees change over time. The crucial factor is that conglomerates, in contrast to aggregates, have a decision procedure for determining group actions [37]. This decision structure transforms the individual intentions and acts into a corporate decision. According to French's argument, the decision structure provides the basis for the attribution of intentionality and, consequently, moral responsibility. In line with French's argumentation, the strategy of the current paper is to assign collective responsibility to those collectives, which have decision-making procedures, including (1) the capacities for forming intentions and (2) the capacities to act. Then, collectives qualify as moral agents and hence can be attributed moral responsibility.

Depending on their size and degree of professionalization, PAOs show the elements of French's approach. Due to the complexities of translational activities and the integration of different subgroups, larger and internationally organized PAOs are highly structured with different levels and positions, such as boards of directors, advisory committees and administration services. In addition, most PAOs have policies, often documented in statutes or mission statements, which make clear whether a decision has been made for corporate reasons. Since PAOs have structures for determining corporate decisions, they can be understood as conglomerates and, according to French's argument, fulfill the conditions of intentionality and moral responsibility.

In addition to the collective dimension of PAOs as subjects of moral responsibility, there is also a future-looking aspect. The prospective dimension of PAOs can be explained in terms of stability and persistence. The PAOs usually have long-term structures and pursue future-oriented goals. Moreover, when understood as conglomerates, the identity of PAOs remains even if the individual members change. Based on these long-term structures, the concept of PAOs as subjects of responsibility can be understood as extending into the future and, consequently, show the forward-looking dimension.

The object

If PAOs are the subjects of responsibility, what are they responsible for? One way to answer this question concerns roles. Roles are often linked to specific behavior and can, therefore, help to narrow down the scope of responsibility. However, the various roles of PAOs lead to different objects of responsibility. Involvement in research, for example, is accompanied by other responsibilities than engagement in politics. However, despite the diversity of PAOs, one mission seems to be common: "Many PAOs characterize their efforts as attempts to give patients a greater voice and ensure that patients' interests are acknowledged by those in positions of power" [10]. The PAOs typically understand themselves as advocates that represent the interests of those affected [1, 3]. This advocacy role of PAOs, although initially self-attributed, is increasingly confirmed by society and policy. The PAOs, for example, are often promoted by political organizations, such as the World Health Organization (WHO) because of their specific function to speak on behalf of patients [55, 56]. Due to this strong weighing, patients' representation and advocacy can be seen as the primary role and, therefore, as the main object of PAOs' responsibility. While this view does not yet provide concrete ethical obligations, it highlights the moral character of PAOs' engagement and can encourage them to emphasize their core values—representing patients and advocating their interests. Responsibilities that are more concrete, for example, regarding certain cooperation partners can build on these basic values.

However, there are several points to consider. Firstly, due to the diversity of the tasks (e.g. policy, education, promoting research) and several interests to be represented within a PAO (e.g. patients, families, carers), it is not straightforward to specify the patient representation by a PAO in a concrete task and it is often unclear who can represent the members of the PAO adequately [17–19]. The object of PAOs' responsibility remains to some degree unspecified because the concrete forms and

implementation of patient representation are manifold, ranging from interaction with individual patients, public communication and educational activities, to political and industry engagement. Secondly, even with such a broad topic as patient representation, a limit to the scope of PAOs' responsibility must be drawn. If issues are not covered or excluded from the domain of PAOs' responsibility, they must be moved to the area of someone else's responsibility in order not to be overlooked. For example, a PAO may set itself the mission of improving patient care for patients with a particular rare disease and, therefore, seek to raise awareness of that disease within medical education. However, it is not the role of the PAO to decide on the content of the medical education or to ensure the quality of the education. This remains the responsibility of the teaching institutions and the medical profession.

Finally, patient representation, for example in health politics, is the result of various activities of multiple agents and is only partially modifiable by PAOs. Consequently, PAOs should not be understood as being responsible for patient representation alone. Other stakeholders in health policy, for example, governments, political organizations such as the WHO and CSOs, whose remit can overlap with that of PAOs, should not be relieved of their responsibilities. For example, a PAO that advocates for a specific rare disease at the regional level and therefore has few members and resources might not be able to carry the overarching responsibility to represent all patients with rare diseases in international health policy. This would lie beyond the scope of that PAO and would instead be the task of international (political) bodies such as the WHO and CSOs advocating on a global level. On the national level, the PAO is also not responsible for the needs of these particular patients alone. National governments, health policy-making institutions, publicly funded healthcare systems and CSOs cannot transfer their responsibility to care for patients with rare diseases to the PAO. Regardless of these points, campaigning for a shared interest bears a collective dimension and since the relevant question "what needs to be done to help those affected?" refers to future activities and states, PAOs' responsibility for patient representation is also prospective in its direction.

The addressee

Having identified what PAOs are responsible for, the question of the addressee remains. Given their advocacy role, it seems acceptable that the addressee of PAOs' responsibility is primarily their targeted (patient) group. However, only considering distinct groups of patients can be too shortsighted in some situations. Issues regarding genetic contexts, for example, might go beyond the patients and affect other individuals or groups. A PAO that supports patients with a genetically determined condition and advocates for genetic testing in childhood or pregnancy should also consider the impact of such testing on families, patient groups with other genetic conditions and society. As this example shows, PAOs are frequently confronted with issues of ethical significance that not only affect their own members but also other groups. If PAOs only take the interests of a certain patient group into account, this can lead to questionable consequences for others. It is, therefore, within the responsibility of PAOs to consider the ethical implications of their activities. This means that PAOs should be committed to a wider range of addressees, however, the question inevitably arises regarding how far the scope of the addressees should extend.

In the context of health policy, for example, Onora O'Neill emphasizes that health issues cannot be restricted to limited groups but need to be considered in a broader context [57]. She claims that measures which are targeted at certain groups can, simultaneously, have collective benefits [57]. O'Neill's idea can be transferred to PAOs: They can be structured in such a way that they produce direct benefit for their defined target group and, in addition, indirect benefit for others. Exemplarily, although a PAO is committed to a specific disease, successfully (co-)funded basic research can help other and future patients. This does not mean that PAOs should override the interests of their target group. An expansion of the addressees, for example, to patients with similar conditions, always needs to be critically assessed. A crucial point is to find a balance between the group's own interests and the interests of other groups. Finding this balance can be especially difficult for PAOs, as PAOs are often built bottom-up. In many cases, PAOs are driven by the individuals affected who often belong to overlooked or discriminated populations. It may be difficult for them to accept that the PAO, which was established to advocate for their specific interests, is now supposed to advocate for the interests of others. However, as argued above, health issues cannot be restricted to limited groups and it is within the responsibility of PAOs to consider the ethical implications to a broader range of potentially affected individuals. Depending on the size and structure of a PAO, the leaders or board members might be in the position to undertake the difficult task of balancing.

Other addressees of PAOs' responsibility could be politicians, scientists and private stakeholders. Although they form a fruitful network for PAOs, such relationships, especially if they are financial, may lead to conflicts of interest and create, for example, biases in PAOs' educational activities [7, 8, 22]. The PAOs that establish such relationships run the risk of becoming financially

dependent and influenced in their activities and might fail to represent the patients' perspective [7, 8, 21, 22]. Due to the frequent lack of independent and adequate resources for PAOs' activities [9], PAOs are often dependent on external funding and, thus, particularly susceptible to dependencies and influences from outside. As long as patient representation is the object of a PAO's responsibility, political, scientific and private stakeholders may be helpful network and cooperation partners for PAOs, but they do not seem to be legitimate addressees of PAOs' responsibility because of the risk of ignoring the advocacy role and pretermitting the interests of the patients. Of course, PAOs have responsibilities towards politicians, scientists and industrial partners when they work together with them, for example, to keep agreements, but these responsibilities are not the subject of the current paper.

When PAOs think about collaboration with politicians etc., they should critically consider their own role and underline their core values—representing patients and advocating their interests. Emphasizing these values highlights the moral character of PAOs' work and the moral character, in turn, creates the basis for the claim that PAOs should not only consider their direct target group but also others in the domain of health. The PAOs are encouraged to go beyond their own interests and to see themselves in a broader social context. Understood in this way, the addressees of PAOs' responsibility covers collective and prospective dimensions.

The normative standard

If responsibility is assigned to PAOs, a normative judgement is rendered on their activities in relation to a normative standard [35]. Typical standards for attributing responsibility are, for example, legal frameworks or ethical principles. Which standard is chosen depends, inter alia, on the concrete situation in which the subject is located, the activities being judged and the type of responsibility (e.g. legal, political or moral) being considered. If PAOs are seen as morally responsible for patient representation and advocacy, the question remains on which standards this can be claimed.

The PAOs' demand for more patient participation in research and health policy has been increasingly recognized both legally and politically in recent decades, particularly in Europe [55, 56, 58–60]. Governments are committed, for example by the WHO, to establishing structures that enable the involvement of groups such as disease-specific advocacy organizations [56]. The way in which PAOs are supported varies greatly from country to country and the legislation is often not properly enforced [9]. However, despite this inconsistent legislative landscape, there is a tendency to see PAOs as responsible for representing the interests of the patients. Institutions, such as ethics councils, also give statements about patient and public participation in healthcare. The British Nuffield Council on Bioethics [61], the French National Consultative Ethics Committee on Health and Life Sciences [62] and the German Ethics Council [63] are examples of these and support patient and public participation as they regularly consult affected groups [64]. Insofar as laws, policies and institutional statements assign PAOs certain tasks and enable them to implement patient participation, they can serve as a normative basis for attributing responsibility for patient representation and advocacy to PAOs.

However, although social and political institutions attribute the responsibility for patient representation and advocacy to PAOs, the assignment of this responsibility comes primarily from the PAOs themselves, because the PAOs have assigned themselves this role. Looking at the PAOs' own statements and constitutions can, therefore, help to identify the normative principles for attributing this responsibility. The constitutions of the PAOs usually define their tasks, missions and core values. Consequently, it would be helpful to examine what role each PAO assigns to itself and which specific responsibilities are associated with this. A PAO that promotes patient advocacy on political committees, for example, has different responsibilities than one that supports patient involvement in clinical trials. Nevertheless, if the common goals and core values behind these specific aims are considered, normative principles can be identified.

The common mission of PAOs to campaign for those affected can often be traced back to the experience of injustice, as many PAOs represent, for example, groups that are stigmatized or diseases that are not sufficiently recognized [1, 3]. One core value that can be identified in the PAOs' statutes is, consequently, social justice. Furthermore, the wish to help each other and the benefits for their own group as well as for others might be strong motivations for PAO members to join their organization. Mutual support and empowerment are values that are strongly represented by the PAOs. By considering the common goals and core values of the PAOs, the principles of justice, beneficence and empowerment emerge. These bioethical principles can capture the PAOs' motivations, form the normative basis for their role and work and therefore for their responsibility. While these principles provide a general ethical orientation, they also leave considerable room for interpretation. Although the principles need to be concretized and weighed against each other in specific situations, PAOs can be encouraged to emphasize these ethical principles in their work and consider the implications of their activities regarding these principles.

If the PAOs are assigned responsibility, a normative standard is needed: Legal and political frameworks, but also the PAOs' own constitutions and the ethical principles of justice, beneficence and empowerment contained therein can be used. Which standards are used may vary depending on the circumstances, in which the PAOs find themselves. The collective dimension can be seen in standards that are the result of a shared deliberative process. The constitutions of PAOs might be assumed to have been elaborated and developed in such a joint process. At least, the ethical principles behind allow room for such processes. If the normative standards also show a long-term orientation, as it is often the case with PAO statements, there is additionally a prospective dimension.

Responsibility as a tool to structure situations

The PAOs can play an important role in the planning and conducting of biomedical research. Many organizations have added contribution to research on their agenda and patients participation, for example, in the design of a research project is usually considered as ethically important in the current bioethical literature [4]. However, PAOs that want to conduce to research find themselves in difficult decision-making situations and are confronted with questions of responsibility. The following example—constructed on debates in the literature and team discussions—demonstrates how the proposed framework of responsibility can serve as a practical tool to structure morally difficult situations (Fig. 1).

A PAO that is committed to rare diseases on a national level receives the invitation to join a clinical trial carried out by a public research institution together with a pharmaceutical company. The PAO could support the study

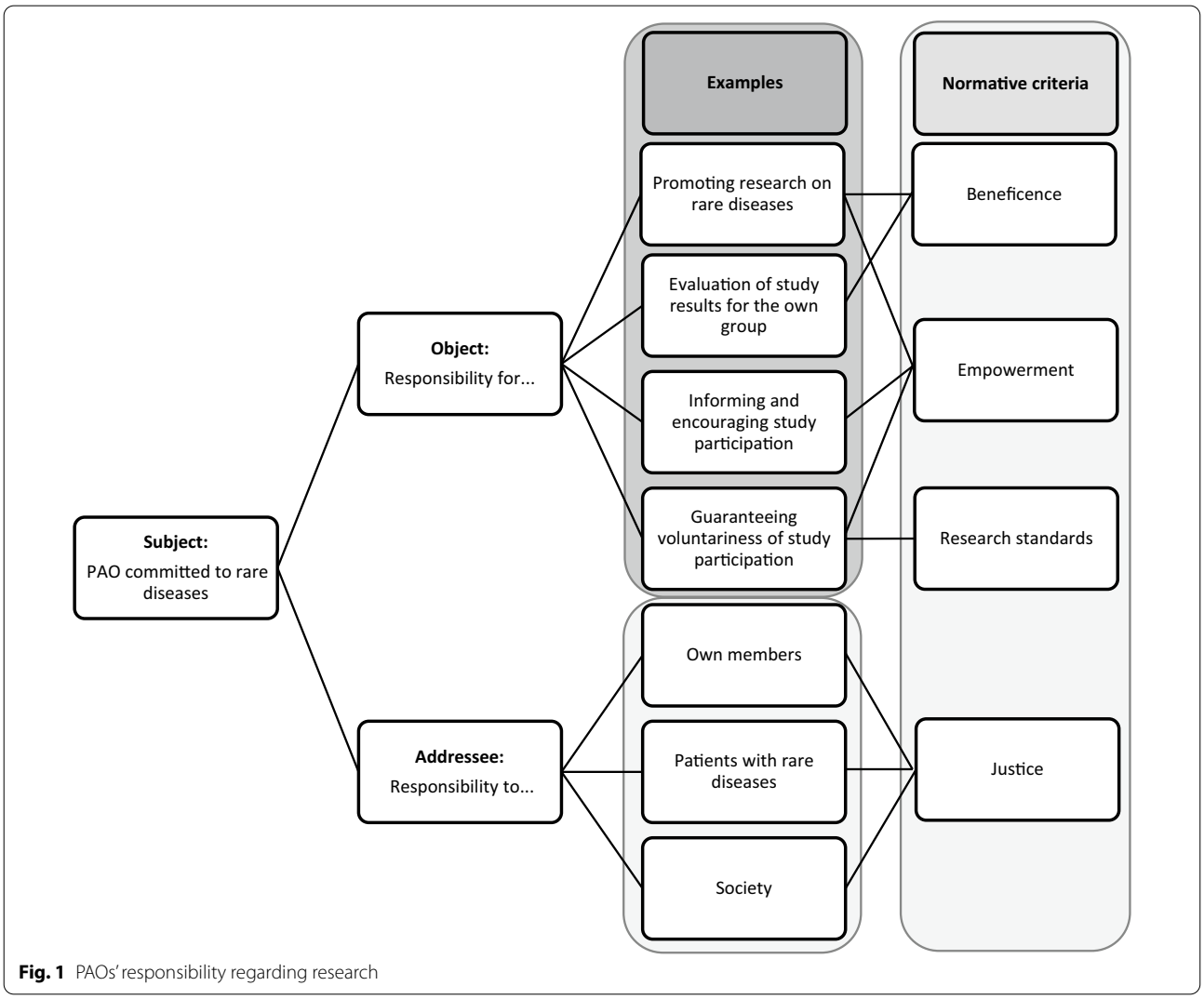

Fig. 1 PAOs' responsibility regarding research

by informing and inviting its members to participate. However, the PAO's officials are unsure whether they should recruit participants for the study. They are questioning for what and to whom the PAO is responsible in such a situation, and which normative principle can justify this responsibility. The outlined framework can help to structure the situation.

Regarding the object, the PAO can emphasize its role: representing persons affected by rare diseases and advocating their interests. These interests consist, at least in the context of research, in promoting studies on rare diseases that result in findings, which helps people regarding diagnosis, therapy or coping with their diseases. It would therefore be the responsibility of the PAO to assess whether the support of this study meets these shared interests. The underlying norm of this responsibility is *beneficence*: the research to be supported is meant to help those affected. If the PAO does not observe the ethical principle of beneficence when selecting the research it wants to endorse and, for example, promotes a study that is not for the benefit of rare disease patients, the PAO may lose the trust of its members and its decision-making power. The principle of *empowerment* complements this obligation, since it is also the responsibility of the PAO to support and empower those affected; which can mean to encourage them to take a (more) active role in research processes. In advertising the study, the PAO would meet this responsibility by informing its members about current research, bringing those affected and scientists closer together and embolden its members to take a position on this research.

When assessing the study, the PAO can also consider *the question of the addressee*: Will the study only serve the group represented by the PAO or will the study have additional collective benefits, for example, for future patients, other social groups or the society? It would be the responsibility of the PAO to include not only its own group but also other addressees in the assessment. The ethical principle behind this responsibility is *justice*. According to this norm, the PAO should consider how access to and benefits of the research are distributed. In line with the PAO's mission, projects that facilitate the development and improve equitable access and distribution of rare disease treatments should be promoted. However, the PAO may consider whether it is worth investing in this individual research project or whether it would be more effective to support the development of research infrastructures in the field of rare diseases in general.

If the PAO decides to forward the invitation to participate in the study to its members, it would be a further responsibility of the PAO to ensure that the members do not feel any pressure to answer this invitation. The underlying ethical principle is *empowerment* or in a broader perspective respect for autonomy. The offer to participate in the study would probably be better accepted by the members if it was offered by the PAO and not by the pharmaceutical company. However, the PAO is responsible for ensuring that the voluntariness of the invitation is guaranteed and that the participants are sufficiently informed about the context of the invitation, for example, about the relationship between the PAO and the research project partners. In addition, the PAO's responsibility to its members can be justified by the Declaration of Helsinki [65], which emphasizes, among other research standards, the voluntariness of research participation.

The aim of this case is to illustrate the application of the four-sided model of responsibility. As the application has shown, the interpretation of responsibility regarding the PAOs' involvement in research is multifaceted and the relata of the model are often interwoven. These ambiguities can be minimised by a precise specification about who is responsible, for what, to whom and on the basis of which ethical standard. An accurate application of the model can help structuring the situation, clarifying the underlying ethical principles and thus contributing to the solution of the conflict. The four-sided model of responsibility, including collective and prospective dimensions, does not claim to be sufficient for all applications, but it can help in structuring and giving orientation.

Conclusions

This contribution provides an analysis of PAOs' moral responsibility. Focusing on the *moral* responsibility directs the attention to the moral character of PAOs' work. PAOs are more than just lobby groups: They are structured in such a way that they are moral agents—hence they are accountable for their actions and have to consider the implications of their activities. The PAOs' task is relatively clear: To represent those affected and stand up for their rights. This can hardly be taken over by an individual but requires collective efforts. PAOs are voluntary groups in society that have accepted the delegation of responsibility for the presentation of patients, therefore, they are answerable to their target groups but also toward others and the society for the successful execution of this and any deficiencies.

By encouraging PAOs to emphasize their core values, the current analysis can help PAOs to find their own position in difficult decision-making situations. The relational responsibility model is a practical analytical tool that can help PAOs to structure situations characterized by question of responsibility and identify the underlying values. Therefore, it can give PAOs general ethical orientation, help them to find their own attitude and establish

clear relationships, for example, with industrial or political agents. Correspondingly, the application of the model can help policy makers, biomedical researchers, and economic stakeholder to understand the roles and responsibilities of PAOs more clearly, which in turn, can help to develop fruitful working relationships with PAOs.

Abbreviations
CSO: Civil society organization; PAO: Patient advocacy organization; WHO: World Health Organization.

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RM, CR and SS conceived the analysis. RM researched literature and wrote the first draft of the manuscript. All authors were significantly involved in the further development of the manuscript. All authors edited the manuscript and approved the final version of the manuscript.

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ORIGINAL RESEARCH

Involving Patient Groups in Drug Research: A Systematic Review of Reasons

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Background: Patients have evolved from mere objects of study to active contributors to drug research in recent decades. Since individual patient's influence to change research processes effectively is limited, patient groups play an important role in the planning and conducting of pharmaceutical studies. Patient group engagement in drug research is usually seen as being beneficial from an ethical viewpoint as well as from the perspective of research practice, while potential disadvantages and risks have been discussed considerably less.

Purpose: A systematic review of reasons was conducted to allow for an overview of the reasons for and against involving patient groups in drug research.

Methods: The literature search was conducted in PubMed and Web of Science. Reasons concerning the influence of patient groups on drug research were extracted and synthesized using qualitative content analysis. The review's main limitation arises from a lack of critical appraisal regarding the quality of the reasons.

Results: A total of 2271 references were retrieved, of which 97 were included in the analysis. Data extraction revealed 91 (73.4%) reasons for and 30 (24.2%) reasons against involving patient organizations in drug research, and 3 (2.4%) ambivalent reasons; amounting to 124 reasons. The main groups of reasons were clustered around the categories: quality of research, acquisition and allocation of resources, and the patient role in research.

Conclusion: This is the first systematic review of reasons concerning the influence of patient groups on drug research. It provides a basis for a continuing debate about the value as well as the limits of involving patient groups. Due to the diversity of research projects there can be no general recommendation for or against patient group involvement. More research is necessary to assess potential advantages and disadvantages of patient groups' influence on other types of research (eg genetics).

Keywords: patient organization, drug research, patient and public involvement, systematic review of reasons, bioethics

Plain Language Summary

Patient groups play an important role in the planning and conducting of pharmaceutical studies. Therefore, their engagement in drug research is usually regarded as being beneficial from both an ethical and a scientific viewpoint. Meanwhile, potential disadvantages and risks of their involvement have received little attention.

For the first time, a systematic overview of the reasons for and against involving patient groups in drug research was created. After identifying relevant literature, reasons concerning the influence of patient groups on drug research were extracted. In total, 2271 references were retrieved, of which 97 contained reasons and were included in the analysis. Data extraction revealed 91 (73.4%) reasons for and 30 (24.2%) reasons against involving patient organizations in drug research, and 3 (2.4%) ambivalent reasons; amounting to 124 reasons.

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By presenting all reasons concerning the involvement of patient groups in drug research, this review provides its readers with a basis to form an educated opinion for the continuing debate about the value and the limits of such an involvement.

Introduction

The involvement of patients and the public in science has become a major factor in the international research landscape.[1–3] Provisions for adequate involvement of patient and public representatives, for example, have become increasingly important for researchers and scientific institutions as a precondition for research funding. In addition, regulatory institutions such as the US Food and Drug Administration increasingly emphasize the importance of patients' input in drug research.[4] The variety of ways in which patients[5] and the public[6] can contribute to research has already been discussed in detail. It ranges from educating patients and the public and building a public opinion, to setting research agendas and supporting the conduct of studies.

The involvement of non-researchers in the research process has been given numerous names, for example, Patient and Public Involvement, patient engagement, public participation and Citizen Science. The way in which and the degree to which patient and public representatives influence the research process vary depending on the conceptual backgrounds. One of the most far-reaching approaches refers to the slogan: "Every participant is a PI".[7] The key idea of this concept is to encourage patients to submit personal health data to an open data repository (like Open Humans[8]) and afterwards to consistently involve them in every step of scientific knowledge production.

In the current literature, there is often no distinction between the involvement of patients and the involvement of the public. However, these differences between patients and the public are important, since each group seems to be driven by different interests.[9] The differing motives may even result in a paradox.[10] Patients can most notably contribute the experience of living with a certain disease – often called "experiential expertise" or "experiential knowledge"[11] – to the development of drugs, distinguishing them from healthy individuals. In addition, they usually have a personal incentive to get involved in drug research for a specific disease, whereas members of the public would rather work towards general improvements in health care.[12] Thus, both a conceptual as well as a practical distinction between the involvement of patients and the involvement of the public seems necessary regarding the epistemic backgrounds and interests of the groups involved.

Another point of controversy relates to the moral value of letting patients participate, for example, in the planning and design of a research project. Patient involvement is usually considered as ethically important in the current literature.[13,14] Some authors see a "compelling ethical rationale [that] supports patient engagement in healthcare research".[5] This "rationale" can, for example, be related to the idea of "epistemic justice". Besides arguing for the inclusion of experiential expertise in knowledge production, "epistemic justice" sees a moral duty in involving patients' perspectives in decisions that will affect primarily patients.[15]

In contrast, discussions about critical aspects have been widely missing, although they deserve just as much attention, as in some cases, patient involvement can be unfavorable.[16,17] A patient organization, for example, can fail to represent the patients' perspective properly and, consequently, promote researchers' rather than patients' interests.[18,19] Another example of a doubtful patient activity is demanding access to unproven and possibly harmful treatments. This creates the risks of resources being spent ineffectively and patient safety being at stake. This has been, for instance, the case with a breast cancer treatment in the 1990s.[20]

Finally, many publications on Patient and Public Involvement are restricted to certain aspects of the phenomenon. Broader assessments of the status quo of functions performed by patients and the public[5,6] and several guidelines on how to implement their involvement[21–23] exist. Seemingly, some researchers are still unsure how patient involvement can be included in their research.[24] A full picture of all reasons for and against patient group (PG) involvement in research has not yet been provided. This can only be achieved through systematic reviews (SRs). This article aims at giving researchers and healthcare decision-makers a comprehensive overview to form their opinions on involving patients in drug research. Due to the different epistemic and normative characters of the involvement of patients or the public respectively, this SR is restricted to patients, and more concretely to PGs. Since individual patient's influence to change research processes effectively is limited, PGs usually function as the major stakeholders in pharmaceutical studies.

Materials and Methods

A SR of reasons[25] with the objective of collecting all reasons regarding the involvement of PGs in drug research was conducted and is reported according to the PRISMA Statement to the extent to which it is applicable to SRs of reasons (see Additional file 1). SRs generally aim to systematically present

all evidence-based knowledge (and lack of such) concerning a specific research question.[26] In recent years, the SR methodology has been adopted and further developed for the field of bioethics, which is characterized by a close connection between normative and empirical research questions.[27] When analyzing argumentative literature, adjustments need to be made to the "classic" SR methodology.[25] There are different types of SRs of argumentative literature, for example, SRs of (ethical) issues, conclusions, concepts, recommendations and reasons.[28] Even if SRs are a rather new methodological approach within the field of bioethics, there have been comprehensive publications on the value of such reviews,[29,30] and several SRs of argumentative literature in general[31] and specifically of SRs of reasons have been already conducted and published.[32–34]

Inclusion Criteria

Two key terms were defined for the search strategy to arrive at a systematic overview of reasons regarding our research objective: "patient groups" and "drug research". We deliberately decided to use broad definitions of our key terms in order to avoid missing any relevant literature. Publications were only considered if they fitted both definitions.

"Patient group", within this review, means any group consisting of patients and/or patient advocates which consistently promotes patients' interests.[35] The activities of individual patients regarding their needs and interests were not included in the review.

Concerning the term "drug research", the review considers all phases of research and development of a medicine product from target identification to clinical Phase III studies as described in the final report of the pharmaceutical sector inquiry of the European Commission.[36]

Groups of patients may have various impacts on medical research. They may, for instance, highly influence the public acceptance and economic feasibility of research. They can also play an important political role or contribute scientifically to research.[37] All these types of impacts were considered in the review if they affected the research and development phases of a drug mentioned above. Only publications in English or German language were included, due to the authors' language capabilities. The search was not limited to a certain time period.

Database Search

After gaining an overview of the existing literature by hand and exploratory database searches, two databases were selected for the systematic search: PubMed and Web of Science. A search strategy was built based on the two key terms – PGs and drug research – and their synonyms. The search term used in PubMed is presented in Box 1. The search was conducted in March 2019.

Box 1 Search Term for PubMed

(((pharmaceutical[Title/Abstract] OR drug[Title/Abstract] OR drugs [Title/Abstract] OR medication[Title/Abstract] OR medicament [Title/Abstract] OR "medicinal product"[Title/Abstract] OR medicines[Title/Abstract]) AND ("research"[MeSH Terms] OR research[Title/Abstract] OR Development[Title/Abstract] OR design [Title/Abstract] OR discovery[Title/Abstract] OR evaluation[Title/ Abstract] OR approval[Title/Abstract])) OR "drug discovery"[MeSH Terms] OR "drug evaluation"[MeSH Terms] OR "drug approval"[MeSH Terms]) AND (("self-help groups"[MeSH Terms] OR self help group[Title/Abstract] OR self help groups[Title/Abstract]) OR (patient organisation[Title/Abstract] OR patient organisations [Title/Abstract]) OR (patient organization[Title/Abstract] OR patient organizations[Title/Abstract]) OR (patient association[Title/Abstract] OR patient associations[Title/Abstract]) OR patient advocacy[Title/ Abstract] OR "patient advocacy"[MeSH Terms] OR patient involvement[Title/Abstract] OR patient engagement[Title/Abstract] OR patient Participation[Title/Abstract] OR "patient participation"[MeSH Terms])

Some of the relevant publications identified via hand search did not appear in the results of our database search, presumably due to their being parts of books. We decided to include them in our study sample to complement the database search results.

Study Selection

Publications which address both of our key terms were included. Two authors, CR and RM, screened the title and abstract of the publications identified via hand and database search and discarded publications not meeting the inclusion criteria. Any disagreement between the two authors was resolved through discourse.

The full texts of the remaining publications were then analyzed regarding their relevance by CR and RM and the results were discussed in regular team meetings. Again, publications not meeting the inclusion criteria were discarded. The remaining publications were included in the review and their bibliographies were screened for additional relevant literature. This resulted in adding further 17 relevant publications to the finally included publications. A flow chart illustrating the study selection is shown in Figure 1.

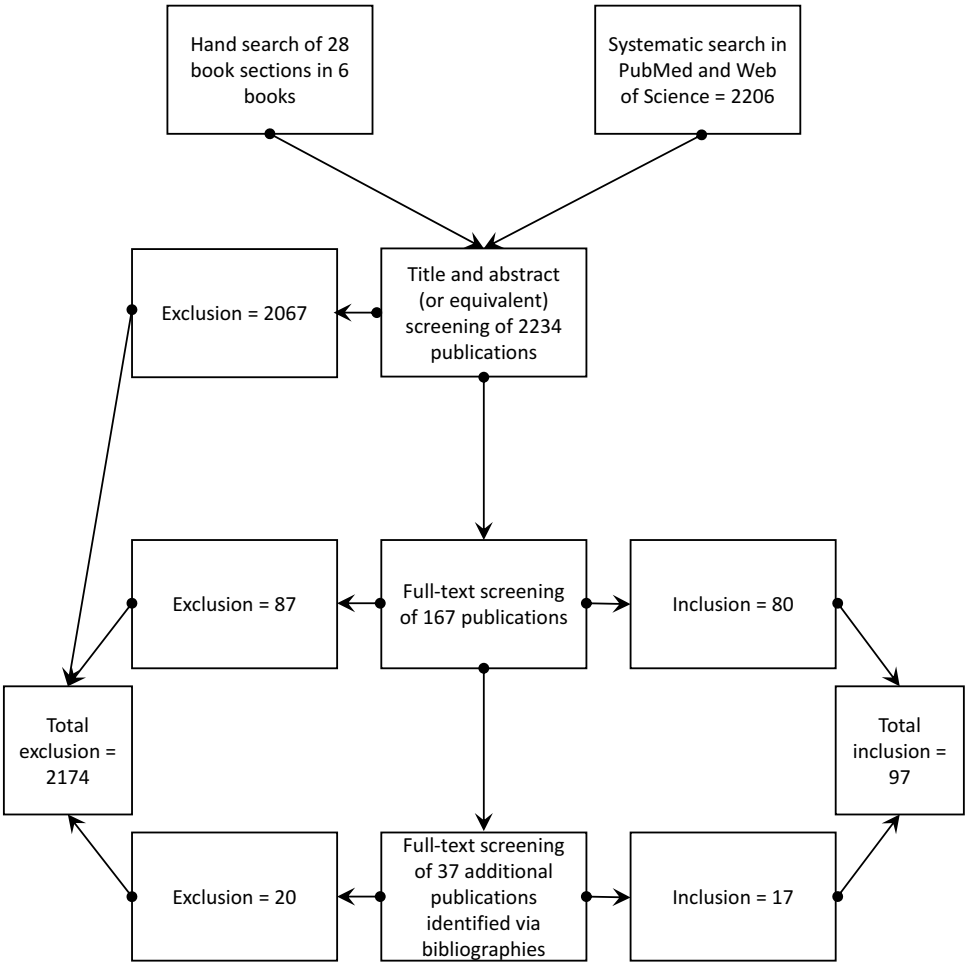

Figure 1 Flow chart of the study selection.

Data Extraction and Qualitative Synthesis

In this review, a reason is understood as the first part of an argument (in this context, often called a "premise"), the second being a conclusion. An argument can consist of multiple reasons/premises that may all lead to one conclusion (eg "the influence of PGs is favorable").[38] This was the case in some of the publications included in the review, as they stated only an "all things considered"-conclusion, but many premises.

Publications were analyzed by two authors (CR and RM) using the method of qualitative text analysis proposed by Mayring,[39] supported by the software MAXQDA Standard 12. According to the research question, the authors screened the publications for reasons regarding the involvement of PGs in drug research. A code was assigned to each occurrence of a reason. Reasons extracted inductively from the material were labeled as narrow reason types. Deductively created categories that condense narrow reason types were labeled as broad reason types. Narrow reasons were analyzed for their alleged implications (pro, contra or ambivalent) regarding the involvement of PGs in drug research.[25] After all the publications had been analyzed once and theoretical saturation was reached, the code system was revised to eliminate doubling and overlapping reason types. All publications were analyzed a second time to ensure the assignment of the correct code from the revised code system for every reason occurrence. Publications were also analyzed for their publication type and their "all-things-considered"-conclusion, which is the final conclusion a publication comes to based on all mentioned reasons.[25]

A quality appraisal of the extracted reasons was deliberately not conducted. Firstly, assessing the quality of a reason is a complex endeavor and can only be achieved by thorough discourse.[38] Methodological standards for quality assessment in SRs of reasons are not available so far.[28] Secondly, the results of such an endeavor depend partly on the context of the particular situation at hand. Therefore, it exceeds the limits of what can be provided in a systematic review of reasons. However, we encourage the readers to assess the quality of reasons presented within the context of their research projects.

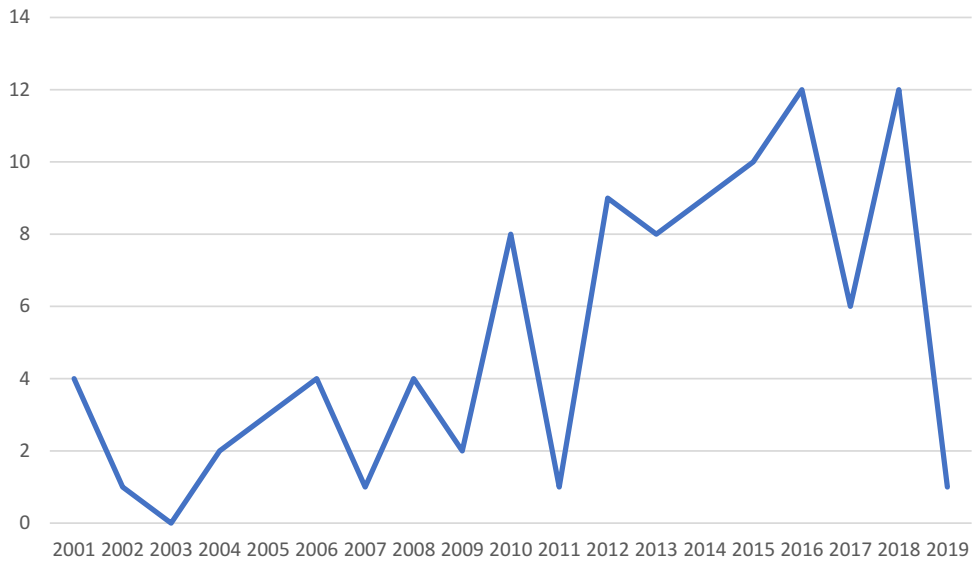

Figure 2 Quantity of publications per year.

Results

A total of 97 publications were finally included from 2271 identified publications during the systematic search. The study sample consists entirely of journal articles and book sections published between 2001 and 2019. Figure 2 shows the number of publications per year. Even though there is some fluctuation, the overall interest in the involvement of patients in drug research is gradually rising. The small number of publications from 2019 is mainly due to the database search being conducted in March 2019.

The study sample is very heterogeneous and shows a wide variety of perspectives of the authors and publication types. Most of the publications focused on rare diseases which leads to the assumption that research on rare diseases benefits greatly from patient involvement. Authors from the pharmaceutical industry were much less interested in patient involvement than patient advocates. The distribution of the authorship possibly contributed to the high number of reasons for the involvement of patients in drug research. The variety of author perspectives is shown in Figure 3 and the quantity of publication

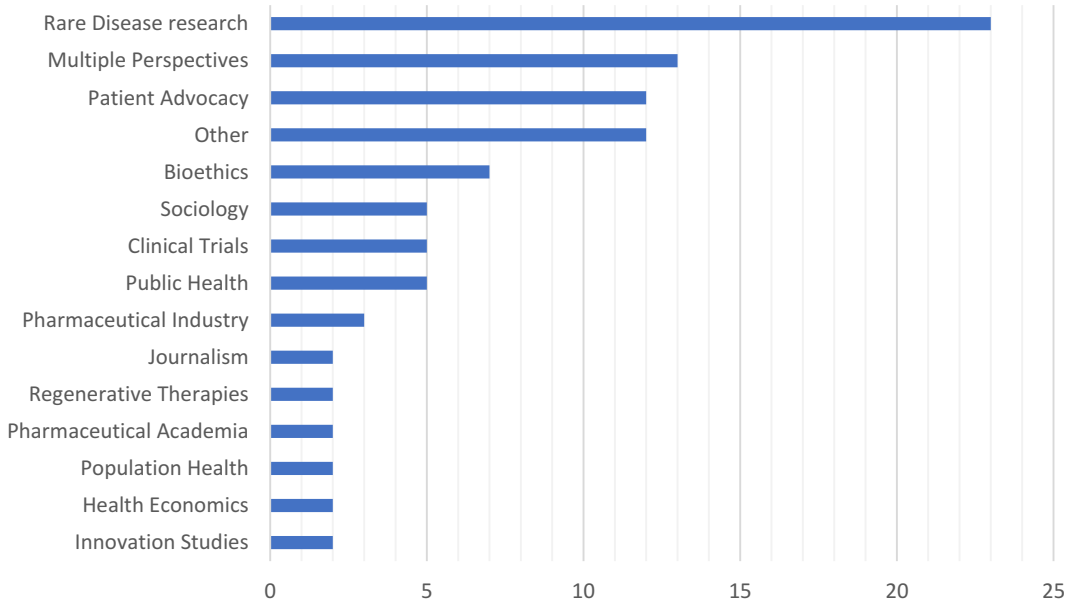

Figure 3 Quantity of authorships' perspectives.

types in Figure 4. All publications were written in English. A list of all publications included is part of the supplementary material of this article (see Additional file 2).

Despite the obvious heterogeneity of the study sample, the "all-things-considered"-conclusions were surprisingly consistent. Most publications drew the conclusion, that the involvement of PGs in drug research is or can be beneficial under certain circumstances. A minority of publications did not have a conclusion. No publication rejected the involvement of PGs entirely. However, publications with occurrences of reasons against the involvement of PGs often warned of risks and dangers, that should be avoided. A summary of the conclusions of all included publications is provided in Figure 5.

Broad Reason Types and Narrow Reason Types

Reasons were categorized during the analysis of the study sample by assigning broad reason types (BRTs) and narrow reason types (NRTs). BRTs summarize NRTs that are closely linked in content. The following six BRTs were identified:

1. Resources: Since resources are limited, many reasons relate to the question whether PGs can acquire, distribute and use resources needed for the research process effectively. Resources discussed include financial investments, research samples, scientific data and time.
2. Collaboration: The creation of new acquaintances and connections between researchers and other stakeholders was generally rated highly for the research process. PGs play a key role in establishing these collaborations.
3. Science: This BRT deals with all reasons concerning quality, conditions, aims and conduct of scientific studies. There are ways in which PGs can influence these parameters either positively or negatively. Setting research agendas is one of the topics mentioned most frequently in this BRT.
4. Patient community: Reasons regarding the quality of patient representation by PGs can be found in this BRT. Possible contributions of patients based on their unique experiences and potential benefits and risks which affect patients directly are also discussed.
5. Ethics: Justification and fairness of research with the involvement of PGs are major reasons in this BRT. PGs' handling of ethical issues is also considered.
6. Public relations: The ability of PGs to promote research-friendly political surroundings and shape the public perception of drug research is subject to reasons in this BRT.

All these six BRTs encompass reasons for and against the involvement of PGs in drug research. Ambivalent reasons can be found in the BRTs *Resources* and *Science*. Table 1

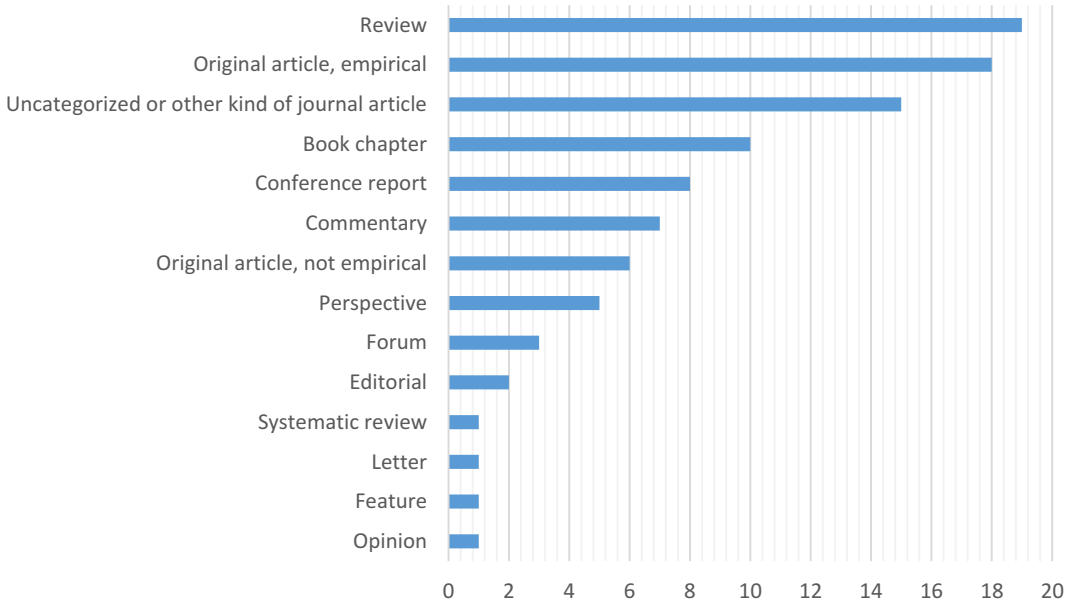

Figure 4 Quantity of publication types.

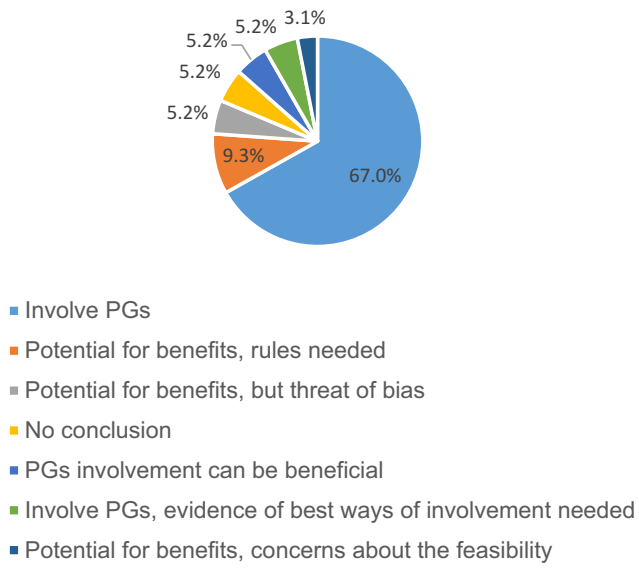

Figure 5 Quantity of "All-things-considered"-conclusions.

shows a detailed list of all reasons, the number of publications each reason occurred in and how the reasons were used. An additional table reveals, which NRTs were found in each included publication (see Additional file 3).

Discussion

As expected, a broad variety of reasons which support the involvement of PGs in drug research was found (91; 73.4%). However, the same applies to reasons against involvement on a smaller scale (30; 24.2%), while only a few reasons were used ambivalently (3; 2.4%). The reason for the discrepancy between pro and contra reasons in this SR is possibly an accurate depiction of a real difference in numbers of respective reasons. However, contra reasons have been mentioned by far fewer publications than pro reasons. Many publications included in this review do not discuss the inclusion of PGs in drug research as their central topic. These articles might tend to address the issue rather superficially and advocate the inclusion of PGs without critical reflection. Publications that cover it as a central topic tend to be more balanced.[19,40,41] They also do not draw their arguments from individual experiences or single examples of good collaboration between PGs and researchers as many of the other publications do. A generalization of these positive experiences is not possible. These findings could indicate that the real cause of the discrepancy is an underrepresentation of contra reasons.

The often-unquestioned ethical rationale whether to involve patients in research is reflected in the NRTs "Patient perspective in research" and "Poor patient representation". Indeed, there are arguments stressing that the status of being affected fundamentally distinguishes healthy people from ill people who, therefore, deserve representation.[42] While most authors agree that this is a desirable goal, some express concerns about whether and how this goal can be achieved by involving PGs. Strategies for addressing these concerns have been rarely discussed so far. One approach could be the analysis of representation and trust models applied by PGs.[43] The concept of a "collective agency"[44] examines the quality of representation in PGs more thoroughly and considers engaging other collective actors like, for example, families. In this concept, four characteristics of collective actors are identified, one of them being building "a shared practice of trust".[44]

The risk of a collaboration with PGs being misused by pharmaceutical companies for commercial purposes is reflected in the NRT "Risk of manipulation by other stakeholders". This risk is especially evident when PGs are being sponsored by companies.[45,46] On the other hand, industrial sponsoring offers opportunities for PGs. This leads to debates with good arguments on both sides.[47,48] The results of this review show that this factor has been used rather rarely as a reason against the involvement of PGs in drug research. Furthermore, it has been acknowledged in every occurrence of the reason that the risk of manipulation can be alleviated by applying preventive measures as, for example, adequate disclosure practices.[49,50]

Limitations

The review is restricted to two databases and a small selection of book chapters identified during hand search. Any other databases, including Google Books, were not considered due to a lack of relevant results in the exploratory searches.

Another limitation is the neglect of literature written in languages other than English and German. One publication (written in Dutch) had to be excluded due to this limitation. The definition of the two key terms and the inclusion of publications and reasons based on them is a crucial point of this review. The definitions developed confine the variety of reasons collected. Moreover, the decision whether a publication or a reason deals with both key terms as part of qualitative data synthesis is subjective. We made these decisions as intersubjectively valid as possible by discussing relevant decisions within the disciplinary research team and solving disagreement by discourse.

Table 1 Reasons For and Against Involving PGs in Drug Research

Reasons	Number of Occurrences	Use of Reason
Resources		
Biological resources		
Acquisition of biological specimen	13	Pro
Biobanks		
Building/Contributing to biobanks	11	Pro
Understanding biomarkers	2	Pro
Competition between PGs over resources	1	Contra
Finances		
Funding		
Funding acquisition of research equipment	3	Pro
Funding basic research	2	Pro
Funding clinical trials	5	Pro
Funding research in general	27	Pro
Funding with personal assets of patients	1	Contra
Leveraging other funding/Reducing risks for other investors	11	Pro
Targeted funding	5	Pro
Raising funds		
Raising funds for basic research	2	Pro
Raising funds for clinical trials	5	Pro
Raising funds from the government	1	Ambivalent
Raising funds in general	19	Pro
Risks of raising funds for unpromising research	1	Contra
Reducing the cost of research	9	Pro
Information		
Collecting research data	12	Pro
Creating patient registries	25	Pro
Disseminating information to patients	32	Pro
Disseminating information to scientists	7	Pro
Removing informational obstacles	3	Pro
Sharing scientific information/data	7	Pro
Providing resources (eg research tools)	11	Pro
Reduction of resources for other activities of PGs	5	Contra
Time investment	5	Contra
Collaboration		
Increasing acquaintances among stakeholders		
Building networks	13	Pro
Connecting researchers	7	Pro
Connecting researchers of different scientific fields	7	Pro
Connecting researchers and patients	7	Pro
Connecting other kinds of stakeholders	3	Pro
Increasing collaboration	28	Pro
Individual approaches of PGs hamper collaborations with them	6	Contra
Influencing attitudes of stakeholders		
Deterring stakeholders from getting involved	1	Contra
Emboldening other stakeholders to get involved	3	Pro
Emboldening scientists to get involved	8	Pro
Organizing conferences	6	Pro
Science		
Clinical Trials		
Acquisition of patients for trials	63	Pro
Organization of clinical trials		
Conduct of trials		
Collecting additional data (eg patient-reported outcome)	7	Pro
Contributing to the evaluation of trials	8	Pro
Enhancing the efficiency of trials	2	Pro
Ensuring patient safety in trials	12	Pro
Organizing/Facilitating clinical trials in general	16	Pro
Trial design		
Contributing to trial design in general	36	Pro
Developing eligibility criteria for trial participation	11	Pro
Improving outcome measures of clinical trials	18	Pro
Improving trial methodology	3	Pro
Convincing physicians to promote trials	2	Pro
Reducing risks of trials		
Paving the way for larger trials with small trials	5	Pro
Reducing risks of trials in general	4	Pro
Offering assistance to participants in trials	5	Pro
Publishing trials	5	Pro
Recommending (or not recommending) clinical trials	2	Ambivalent
Conditions for research		
Making research less attractive for scientist	2	Contra
Changing the research environment	6	Pro
Creating opportunities for innovation	3	Pro
Creating surroundings for effective research	5	Pro
Development process		
Acceleration of drug development	26	Pro
Contributing to the development of spin-off products	2	Pro
Creating new (so far unknown) risks for the development process	1	Contra
Direct scientific contributions of PGs	9	Pro
Enabling more focused research	1	Pro
Flexibility in the research process	2	Pro
Giving preference to clinical evaluation over basic research	2	Pro
Repurposing therapeutics	4	Pro
Simplifying the development process by retaining property rights	1	Pro
Supporting advance in research	17	Pro
Testing unproven therapeutics on group members	1	Ambivalent
Translating scientific knowledge into therapeutics	11	Pro
Increasing participation in research	10	Pro

(*Continued*)

Table 1 (Continued).

(*Continued*)

Table 1 (Continued).

Reasons	Number of Occurrences	Use of Reason
Initiation of research		
Commissioning necessary studies	2	Pro
Starting research projects	8	Pro
Quality of research		
Improper handling of biological material	1	Contra
Increasing effectiveness and sustainability of medicines	18	Pro
Increasing the reliability of research results	2	Pro
Ineffective research due to misunderstandings regarding roles	2	Contra
Lack of evidence of the value of patient involvement	1	Contra
PG's lack of scientific knowledge reduces the quality of research	9	Contra
Poor quality of studies due to the involvement of PGs	5	Contra
Reducing bias in research	2	Pro
Supporting evaluation of research results	2	Pro
Research agenda		
Considering unconventional therapeutics, eg natural medicine	1	Pro
Coordinating research	9	Pro
Increasing the amount of research conducted	1	Pro
Identifying unmet medical needs	7	Pro
Reconciling research needs	2	Pro
Setting research priorities	27	Pro
Supporting scientists	12	Pro
Patient community		
Benefits for patients		
Access to investigational drugs	6	Pro
Creating hope for patients	2	Pro
Involvement in research strengthens patient communities	1	Pro
Involvement is a way of coping with individual hardships	1	Pro
Leading to health benefits for patients	11	Pro
Contributions of patients based on their experiences		
Experiential expertise	25	Pro
Experiential expertise is insufficient	3	Contra
Personal affliction can be a driving force in research	4	Pro
Personification of disease	4	Pro
Representation of patients		
Patient representation/perspective in research	36	Pro
Risk of poor patient representation	17	Contra
Risks		
Creating unrealistic hopes	2	Contra
Endangering patients by advocating possibly harmful drugs	5	Contra
Improper handling of patient data	1	Contra
Inappropriate motives of patients despite affliction		
Risk of manipulation by other stakeholders	8	Contra
Suspicion of conflicts of interest/bias	19	Contra
Ethics		
Alluring participants with money	2	Pro
Creating social pressure to participate	1	Contra
Dealing with research advances	1	Pro
Deliberately neglecting ethical issues in research	3	Contra
Disagreement over ownership of findings	1	Contra
Justice		
Epistemic justice	1	Pro
Ethical justification of research	1	Pro
Increasing democratic value	6	Pro
Increasing undue preference of certain research interests	11	Contra
Unjust allocation of resources	2	Pro
Pointing out ethical issues in research	4	Pro
Promoting confidentiality protections for participants	3	Pro
Restricting academic freedom of scientists	1	Contra
Public Relations		
Contributing to favorable policies/legislation for research	12	Pro
Creating unrealistic hopes	3	Contra
Exploiting sick children to raise public awareness	1	Contra
Increasing patients' trust in research	7	Pro
Increasing public debates/awareness	14	Pro
Influencing public attitude towards research negatively	1	Contra
Overly positive presentation of results	2	Contra

Notes: The six BRTs are shown as headlines in bold text. The column "Reasons" lists all reasons extracted from the data, "Number of occurrences" shows how many publications mentioned each reason and "Use of reason" indicates the alleged implication of the reason ("Pro" indicating reasons for and "Contra" indicating reasons against involvement). BRTs do not have a "Number of occurrences" and a "Use of reason" but encompass the following indented NRTs.

Conclusion

The results of this review indicate that the inclusion of PGs in research can be fruitful. Nevertheless, due to the variety of PGs, no general recommendation to involve or not involve PGs in drug research can be made from this SR of reasons. The reasons presented should, however, be considered carefully when thinking about such a collaboration. Leaders of PGs, for example, can decide whether their PG should get involved in drug research or if patients' interests can be promoted better if resources are spent on other PG activities.

Similarly, leaders of pharmaceutical companies can decide whether engaging PGs in their specific research field is likely to favor the research process. Policy-makers can use this review to create new policies that will improve the conditions for research landscapes.

The reasons presented in this review refer specifically to PGs and drug research. Although they can certainly be adapted to other contexts, there is a need for more SRs assessing reasons for patient involvement relating to other fields of research as, for example, genetics research.

Abbreviations

PG, patient group; SR, systematic review; BRT, broad reason types; NRT, narrow reason types.

Availability of Data and Material

A list of all publications included in the SR and a detailed list of all reason type occurrences in each publication are part of the additional material. Further data and material can be requested from the first author.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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