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Ethische Aspekte der genetischen Testung auf seltene Erkrankungen

Eine multimethodische Untersuchung mit spezieller Berücksichtigung der hereditären chronschen Pankreatitis

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II. Abkürzungsverzeichnis

EU	Europäische Union
USD	US Dollar
NGS	Next generation Sequencing
PRSS1	Protease serine1
SPINK1	Serinprotease-Inhibitor Kazal Typ 1
CTRC	Chymotrypsin C
HCP	Hereditäre chronische Pankreatitis

1. Einleitung

1.1 Seltene Erkrankungen

In der Europäischen Union gilt eine Erkrankung als selten, wenn weniger als 5 von 10.000 Personen von ihr betroffen sind (1). Weltweit haben 400 Millionen Menschen eine seltene Erkrankung, in der EU sind es insgesamt 29 Millionen Menschen (1).

Die Seltenheit einer Erkrankung ist mittlerweile mehr als eine reine Tatsachenbeschreibung. Bis Ende der 1960er Jahre wurde der Begriff „seltene Erkrankung“ nur zur Beschreibung einer Charakteristik einzelner Erkrankungen verwendet (2). Die Plural-Form zur Beschreibung einer abgrenzbaren Gruppe findet erst seit den 1970er Jahren zunehmende Verwendung. Gefördert durch den Einsatz von Patient*innenorganisationen und Verbänden, wurde dieser Ausdruck erstmalig 1984 in einer zweiten Version des US Amerikanischen *Orphan Drug Act* definiert (2,3). Ziel des *Orphan Drug Acts* und anderer vergleichbarer Erlasse ist es, Anreize für die Industrie zu schaffen, um Medikamente mit geringen Gewinnspannen auf dem Mark zu ermöglichen (4). Darüber hinaus sollen Forschung und Innovationen auch trotz der teils sehr geringen Fallzahlen seltener Erkrankungen und der damit verbundenen geringen wirtschaftlichen Rentabilität gefördert werden (4). Daraus ergeben sich mit der Einordnung einer Erkrankung als selten versorgungsrelevante und politische Besonderheiten.

Seltene Erkrankungen haben jedoch mehr Gemeinsamkeiten als geringe Fallzahlen. Ein häufig beschriebenes Phänomen ist die sogenannte Diagnostische Odyssee. Eine Diagnostische Odyssee beschreibt einen durchschnittlich 8 Jahre andauernden Prozess, bestehend aus einer Vielzahl an Arzt- und Klinikbesuchen sowie unter Umständen multiplen Verdachts- und Fehldiagnosen, welcher mit der Diagnose einer seltenen Krankheit endet (5). Diese andauernde Unsicherheit stellt eine psychische Belastung für Betroffene und aufgrund der langwierigen und teils invasiven Untersuchungen auch eine physische und finanzielle Herausforderung dar. Zusätzlich kostet diese Diagnostische Odyssee nicht nur Zeit, sondern das US-Gesundheitssystem pro Patient*in mindestens 10.000 USD jährlich (6).

Es wird davon ausgegangen, dass bis zu 80 Prozent der seltenen Erkrankungen genetische Ursachen haben (5). Daher können auch ganze Familien oder sogar ethnische Gruppen von einer seltenen Erkrankung betroffen sein. Technologische Innovationen in der Identifikation genetischer Krankheitsursachen, wie *Next Generation Sequencing*, stellen mittlerweile einen Schlüs-

sel zu einer schnellen und sicheren Diagnose dar (5,7,8). Dadurch kann die Diagnostische Odyssee deutlich verkürzt werden und unnötige und unter Umständen invasive Tests und Prozeduren vermieden werden. Auch der psychologische Stress, welcher mit einer unklaren Diagnose verbunden ist, kann reduziert werden (7,8).

1.2 Hereditäre chronische Pankreatitis

Eine seltene genetische Erkrankung, welche im Folgenden genauer betrachtet wird, ist die hereditäre chronische Pankreatitis (HCP), eine seltene Form der chronischen Pankreatitis. Die Prävalenz liegt bei 1/800.000 in Deutschland (9). Die HCP ist charakterisiert durch einen langfristigen Verlust der exokrinen und endokrinen Pankreasfunktionen gepaart mit wiederkehrenden Episoden akuter Pankreatitiden (10). Auf genetischer Ebene kann die hereditäre Pankreatitis durch verschiedene Mutationen hervorgerufen werden, am häufigsten über eine Mutation in dem Risiko Gen PRSS1, seltener auch in den Gensequenzen SPINK1 oder CTRC, welche zumeist autosomal dominant vererbt werden und eine variable Penetranz aufweisen (10,11). Die Krankheit verläuft sehr unterschiedlich, Symptome reichen von abdominellen Schmerzen mit Übelkeit und Erbrechen über die Bildung von Pseudozysten des Pankreas bis hin zum Verschluss der Gallengänge und einem erhöhten Risiko für Pankreaskarzinome (12,13). Meist verläuft sie in akuten Schüben. Der individuelle Verlauf ist wenig vorhersehbar und durch die damit verbundene Unsicherheit eine große Belastung für die Patient*innen und deren Familien (14,15)).

Bisher ist wenig bekannt zu den sozialen Folgen und ethischen Herausforderungen, welche mit einer HCP Erkrankung verbunden sind. Insbesondere der familiäre Kontext ist wenig untersucht. Gleichzeitig fehlen Übersichtsarbeiten zu ethischen Aspekten bei seltenen Erkrankungen, insbesondere im Kontext der genetischen Testung. Diese können helfen, Erfahrungen mit einzelnen seltenen Erkrankungen zu vergleichen und in einen größeren Kontext zu setzen.

1.3 Ziel der Arbeit

Der vorliegenden kumulativen Dissertation liegen drei Publikationen zugrunde:

Müller 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. 2022;18(4):818-33. (16)

Müller 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. 2021;29(1):29-38. (17)

Kruse J, Müller R, Aghdassi AA, Lerch MM, Salloch S. Genetic Testing for Rare Diseases: A Systematic Review of Ethical Aspects. Front Genet. 2021;12:701988. (18) [1]

Die dieser kumulativen Dissertation zugrundeliegenden Publikationen wurden in zwei Schritten erarbeitet. Erstens wurden am Beispiel der HCP die Erfahrungen von Patient*innen mit einer seltenen Erkrankung genauer untersucht. Zu diesem Zweck wurde eine Interviewstudie mit HCP Patient*innen und deren Angehörigen anhand von semistrukturierten Einzelinterviews durchgeführt, in denen das subjektive Erleben der Erkrankung explorativ erhoben wurde. Dabei wurden genetische Tests als ein besonders zentrales und komplexes Thema identifiziert. Folglich wurde ergänzend zu den Interviews eine Fokusgruppe durchgeführt, in der die Erfahrungen mit genetischen Tests genauer besprochen wurden.

Als zweiter Projektteil wurde ein systematisches Literaturreview durchgeführt, um ethische Aspekte zu genetischen Tests bei seltenen Erkrankungen umfassend und systematisch abzubilden.

Das Ziel dieser Studie ist es, die psychosozialen und ethischen Bedeutungen des Lebens mit einer seltenen, chronischen Erkrankung zu erfassen, um deren Auswirkungen besser einordnen zu können. Zur umfassenden Abbildung des psychosozialen Kontexts wurden die Erfahrungen der Patient*innen ergänzt um die Perspektiven der Angehörigen. Die Interviewstudie wurde in zwei Publikationen ausgewertet: in „Lived Experience of Hereditary Chronic Pancreatitis – A Qualitative Interview Study“ (16) wurde die subjektiven Erfahrung von Patient*innen und Familienangehörigen mit HCP anhand von biografischen Konzepten aus der Literatur untersucht. In „Perceptions of genetic testing in patients with hereditary chronic pancreatitis and their families: a qualitative triangulation“ (17) wurden zusätzlich zu den Interviews in einer Fokusgruppe die Erfahrungen mit genetischen Tests zu seltenen Erkrankungen ausgewertet.

[1] Diese Arbeit wurde im Rahmen des Projekts „PEPPP – Proteinfehlfaltung, ER-Stress und Proteindegradation“ im Projektteil 8 „Ethische Aspekte der Patientenselbsthilfe“ durchgeführt. Ziel des PEPPP-Projektes ist die Entwicklung einer systematischen Pipeline für individualisierte Therapien bei erblicher Leber- und Pankreaserkrankungen. Dieses Forschungsprojekt wurde im Rahmen der Landesexzellenzinitiative Mecklenburg-Vorpommern von der Europäischen Union gefördert.

Das Ziel des systematischen Reviews ethischer Aspekte zu genetischen Tests bei seltenen Erkrankungen war es, einen umfassenden Überblick ethischer Aspekte aus der publizierten Literatur zu erlangen. Mehr als die Beantwortung einer spezifischen normativen ethischen Frage, sollte das Review eine möglichst vollständige Darstellung der in der Literatur genannten Aspekte ermöglichen. Damit bietet es eine systematische Übersicht ethischer Aspekte vom Mikro-Level wie Arzt-Patient*innen-Kontakt bis hin zum Makro-Level wie die Struktur der Gesundheitssysteme. Das systematische Review „Genetic Testing for Rare Diseases: A Systematic Review of Ethical Aspects“ (18) ist die dritte dieser kumulativen Dissertation zugrundeliegende Publikation.

2. Methoden

Es folgt eine Kurzdarstellung der Methodik der zwei Projektteile. Eine detailliertere Beschreibung ist den jeweiligen Publikationen zu entnehmen (16–18).

2.1 Methoden der Interviewstudie

2.1.1 Studiendesign

Um die übergeordnete Studienfrage nach den Erfahrungen der von HCP betroffenen Patient*innen und ihren Familien zu beantworten, wurde ein exploratives, qualitatives Studiendesign (semistrukturiertes Interview) ausgewählt (19). Als theoretischer Rahmen wurden vorab verschiedene Konzepte festgelegt. Das erste Modell entspricht einem Paradigma der Forschung zu chronischen Erkrankungen, dem Konzept der *biographical disruption* von Bury (20). Dieses Konzept beschreibt eine chronische Erkrankung als einschneidendes Erlebnis und definiert eine Zeit vor und eine Zeit nach der Erkrankung (20). Da dieses Konzept auf Grund seines Mangels an Differenziertheit zunehmend kritisiert wird, wurde es ergänzt durch das Modell der *shifting perspectives* von Paterson (21). Dabei wird eine chronische Erkrankung als ein andauernder, sich kontinuierlich verändernder Prozess begriffen, in dem sich Phasen von Gesundheit und Krankheit abwechseln. Ergänzend wurde auch das Modell der *biographical contingency* berücksichtigt, wobei ein weitestgehend „normales“ Leben im Vordergrund steht, in dem die chronische Krankheit phasenweise Einschnitte verursacht (22).

2.1.2 Erstellung der Interviewleitfäden

Die Interviewfragen wurden schrittweise entwickelt. Zunächst wurden basierend auf der aktuellen Literatur zu HCP und den Erfahrungen des Forschungsteams zu der Thematik Fragen

zusammengetragen. Diese wurden ergänzt um Fragen basierend auf der theoretischen Literatur zu chronischen Erkrankungen. In einem zweiten Schritt wurden die Fragen auf ihre Eignung geprüft und Themenbereichen zugeordnet. Daraus wurden zwei Interviewleitfäden erstellt, einer für Patient*innen und einer für Angehörige. In einem letzten Schritt wurden die Leitfäden in je einem Pilotinterview überprüft und nachfolgend angepasst.

Der Interviewleitfaden basiert auf vier zentralen Themen: 1.) Patient*innenbiografie, 2.) Erfahrung mit genetischen Tests, 3.) biomedizinische Forschung und 4.) Patient*innenselbsthilfegruppen. In den Einzelinterviews wurden genetische Tests als ein zentrales Thema identifiziert und dies folglich als Vertiefungsthema im Gesamtprojekt festgelegt.

2.1.3 Qualitative Triangulation

Eine Triangulation kombiniert verschiedene wissenschaftliche Herangehensweisen, ein Objekt zu untersuchen und kann unterschiedliche Aspekte der Datenerhebung, Auswertung, Theorien und Methodik beinhalten. Dabei ist das Ziel, ein möglichst vollständiges Bild des Forschungsgegenstandes zur erlangen (23). In dieser Studie wurde eine Methodentriangulation genutzt. Die Einzelinterviews wurden dabei bezüglich des Vertiefungsthemas ergänzt durch eine Fokusgruppe. Eine Fokusgruppe stellt eine moderierte Gruppendiskussion anhand eines zuvor festgelegten Leitfadens dar (24). Auf der gleichen Basis wie für die Einzelinterviews wurde auch für die Fokusgruppe ein Leitfaden erarbeitet.

2.1.4 Auswahl der Studienteilnehmer*innen für Einzelinterviews und Fokusgruppe

Die Teilnehmer*innen der Interviews sind mehrheitlich Mitglieder der deutschen Selbsthilfegruppe Deutsche Pankreashilfe e.V., in der auch Patient*innen mit HCP und deren Familien vertreten sind. Über die Organisation wurde eine Einladung zur Teilnahme an dieser Studie versendet. Interessierten Mitgliedern wurde Informationsmaterial über die Interviewstudie zugesendet und Fragen in einem telefonischen Gespräch geklärt. Die Mitglieder der Patient*innenorganisation wurden darüber hinaus gebeten, die Einladung zur Teilnahme mit anderen Interessierten zu teilen, um nach einem Schneeballprinzip weitere Teilnehmende zu gewinnen.

Einschlusskriterium war, dass die Teilnehmenden sich selber als HCP Patient*innen bzw. als Träger der PRSS1 Mutation oder Angehörige von mindesten zwei betroffenen Familienmitgliedern identifizieren und mindesten 18 Jahre alt waren. Angestrebt wurde eine hinsichtlich des

Alters, Geschlechts, Bildungsniveau und Krankheitsprogress möglichst vielfältige Studienpopulation.

2.1.5 Datenerhebung

Die semistrukturierten Einzelinterviews wurden im Zuhause der Patient*innen oder telefonisch durchgeführt. Während des Gespräches wurden Notizen erstellt. Zusätzlich wurden die Interviews aufgezeichnet, wörtlich transkribiert und pseudonymisiert. Als Ergänzung fand die Fokusgruppe statt. Auch diese wurde aufgezeichnet, wörtlich transkribiert und pseudonymisiert.

Die Datenerhebung wurde beendet, als eine Sättigung der Daten erreicht wurde. Die Datensättigung wurde als der Punkt definiert, ab dem keine neuen, relevanten Erkenntnisse mehr gewonnen wurden und sich die Ergebnisse wiederholten (25).

2.1.6 Datenauswertung

Die Auswertung der Transkripte wurde entsprechend der Prinzipien der qualitativen Inhaltsanalyse nach Mayring (26) durchgeführt. Die Transkripte wurden mit Hilfe der Software MAXQDA12 codiert und kategorisiert. Schriftliches Einverständnis wurde vor den Interviews von allen Studienteilnehmenden eingeholt. Die Studie wurde von der Ethikkommission der Universitätsmedizin Greifswald unter der Referenz BB074/17 positiv begutachtet.

2.2 Methoden des Systematic Review

2.2.1 Suchstrategie

Nach einer Probesuche wurden die Datenbanken *Pubmed*, *Science Direct* und *Web of Science* als die relevantesten identifiziert und mit systematischen, zuvor festgelegten Suchbegriffen durchsucht. Die Ergebnisse wurden heruntergeladen und die Duplikate entfernt. Diese Datenbanksuchen wurden im Juni 2020 durchgeführt. Beschränkt wurde die Suche auf Ergebnisse in englischer und deutscher Sprache.

Web of Science	*TS=(ethic*) AND TS=((rare disease*) OR (orphan disease*)) AND TS=(genetic test*)*
ScienceDirect	*("rare disease" OR "rare diseases" OR "orphan disease" OR "orphan diseases") AND ("genetic test" OR "genetic testing") AND (ethics OR ethical); Title/Abstract/Key Words: ethics OR ethical*
PubMed	*((rare disease[MeSH Terms]) OR (orphan disease[MeSH Terms]) OR ("rare disease*"[Title/Abstract]) OR ("orphan disease*"[Title/Abstract])) AND ((genetic testing[MeSH Terms]) OR (predictive genetic testing[MeSH Terms]) OR ("genetic test*"[Title/Abstract])) AND ((ethic*[Title/Abstract]) OR (ethics[MeSH Terms]))*

Abbildung 1 Search String

2.2.2 Auswahlkriterien

Als Auswahlkriterium zur Berücksichtigung einer Publikation in dem systematischen Review wurde die Beschreibung einer oder mehrerer ethischer Aspekte zu genetischen Tests bei seltenen Erkrankungen definiert.

Ethische Aspekte wurden auf der Basis der Prinzipienethik nach Beauchamp und Childress definiert (27). Bei diesem Ansatz werden vier gleichwertige Kernprinzipien berücksichtigt: Respekt für Autonomie, Nicht-Schaden, Wohltun und Gerechtigkeit. Diese vier Prinzipien dienen der Orientierung und sollten befolgt werden, solange sie nicht im Konflikt zu einander stehen. Im Konfliktfall sollen die Prinzipien im Kontext der gegebenen Situation gegeneinander abgewogen werden. Somit kann ein ethischer Konflikt entstehen, wenn in einer spezifischen Situation ein oder mehrere der Prinzipien nicht ausreichend berücksichtigt werden (zum Beispiel das kindliche Recht auf Nichtwissen bei einer pränatalen Gendiagnostik) oder wenn zwei oder mehrere Prinzipien im Widerspruch zueinanderstehen (zum Beispiel, wenn ein genetischer Test eine Therapie ermöglicht und gleichzeitig eine negative gesellschaftliche Stigmatisierung mit sich bringt) (28).

Genetische Tests wurden definiert als eine laborchemische Untersuchung mit dem Ziel, erbliche Erkrankungen oder Prädispositionen durch eine direkte oder indirekte Analyse des genetischen Materials (z.B. Gene, Chromosomen, Proteine) zu diagnostizieren (29).

Bis zur Fertigstellung dieser Arbeit existierten keine definierten Kriterien zur Qualitätssicherung qualitativer Datenauswertungen im Rahmen systematischer Reviews ethischer Literatur (30). Demzufolge wurde in diesem Review keine Qualitätsprüfung der eingeschlossenen Quellen durchgeführt.

2.2.3 Auswahl der Publikationen

An den in den Datenbanken gefunden Texten wurde ein Titel Abstract Screening durchgeführt. Wenn Publikationen den Einschlusskriterien entsprachen, wurde als zweiter Schritt eine Analyse des Gesamttextes durchgeführt. Wenn die Publikation im Sinne der Fragestellung relevante ethische Aspekte enthielt, wurde sie in das Review aufgenommen. Nach Einschluss aller Dokumente wurde ein Screening der Literaturverzeichnisse der eingeschlossenen Literatur nach dem Schneeballprinzip durchgeführt, um zusätzliche Publikationen zu identifizieren.

2.2.4 Extraktion ethischer Aspekte

Auch im Falle des Reviews wurde die Datenanalyse nach dem Prinzip der qualitativen Datenanalyse nach Mayring durchgeführt (26). Dazu wurde die Software MAXQDA12 genutzt. Die Publikationen wurden gescreent auf die relevanten ethischen Aspekte. Jedem dieser Aspekte wurde ein beschreibender Code zugeordnet. Diese induktiven Codes wurden in einem zweiten Schritt aus dem Textmaterial heraus entwickelt und den deduktiven Kategorien zugeordnet.

3. Ergebnisse

3.1 Ergebnisse der Interviewstudie

Die qualitative Interviewstudie wurde zwischen Juli 2017 und Oktober 2019 in Deutschland durchgeführt. Insgesamt wurden 28 Personen in die Studie eingeschlossen. Zwei potentielle Teilnehmende lehnten das Interview aus persönlichen Gründen ab. Es wurden 22 semi-strukturierte Einzelinterviews durchgeführt (davon 17 mit Patient*innen und sieben mit Angehörigen). Vier Personen (zwei Patient*innen und zwei Lebenspartner*innen) nahmen an der Fokus-

gruppe teil. In dieser Studie sind Patient*innen in verschiedenen Stadien der Erkrankung eingeschlossen, dabei befand sich eine Person zum Interviewzeitpunkt in einem aktiven Schub der Erkrankung.

Von den Einzelinterviews wurden 20 im Zuhause der Teilnehmenden durchgeführt. Zwei Interviews fanden telefonisch statt. Die Fokusgruppe wurde im Rahmen der jährlichen Versammlung der Selbsthilfegruppe abgehalten.

Durch die eigenständige Rollenzuteilung der Teilnehmenden kamen drei Kategorien zustande: Patient*in, Partner*in und Elternteil. Einige Teilnehmende haben sich mehrere Rollen zugeschrieben. Dadurch bildet die Studie verschiedene, eng miteinander verwobene Familienbeziehungen ab. Zur Wahrung der Übersichtlichkeit wurde nur eine formale Rolle pro teilnehmender Person verteilt.

3.1.1 Genetische Tests

Da genetische Tests ein zentrales Thema in den Interviews darstellen, wurde dieses Thema in der Fokusgruppe weiter vertieft. Im Folgenden werden ausgewählte Studienergebnisse vorgestellt. Die Erfahrungen mit genetischen Tests durch HCP Patient*innen und ihre Familienangehörigen stehen dabei im Vordergrund. In den Interviews wurden drei übergeordnete Themen festgelegt und in der Fokusgruppe ausführlich diskutiert: genetische Tests in der Kindheit, genetische Tests, die Familien gemeinsam durchgeführt haben, und Familienplanung.

3.1.2 Genetische Tests in der Kindheit

Genetische Tests in der Kindheit wurden sowohl in Bezug auf Tests in der eigenen Kindheit sowie Tests bei den eigenen Kindern diskutiert. Nicht allen Teilnehmenden war klar, ob der erste Test schon in der Kindheit durchgeführt wurde und ob ihnen das Ergebnis mitgeteilt wurde.

Viele Teilnehmende waren sich unsicher, wie sie selbst mit der Erfahrung eines genetischen Tests in ihrer Kindheit umgehen sollten. Bezüglich des idealen Zeitpunktes und Alter zur Testdurchführung bestand Einigkeit darüber, dass dies eine individuelle Entscheidung sein sollte und der richtige Zeitpunkt nicht allgemein festgelegt werden kann. Die Jugend wurde von den meisten Teilnehmenden als der angemessenste Zeitpunkt genannt. Als Gründe gegen eine frühere Testung wurden die fehlende Lebenserfahrung und das fehlende Verständnis für die

Konsequenzen des Testergebnisses aufgeführt. Ein Test direkt nach der Geburt wurde abgelehnt. Dabei konnte kein Unterschied zwischen Patient*innen und Angehörigen festgestellt werden.

Darüber hinaus wurde die Verantwortung der Eltern diskutiert. Einige fanden es besonders wichtig, dass die Eltern von der Erkrankung der Kinder wissen sollten, um entsprechend mit den Kindern umgehen zu können. Darin wurden aber auch mögliche negative Konsequenzen für die Kinder gesehen, da die Eltern zu übertriebener Vorsicht neigen könnten.

Einige Patient*innen berichteten, selbst überzogene Vorsichtsmaßnahmen in ihrer Kindheit erlebt zu haben, wodurch sie das Gefühl hatten, dass ihnen die Teilhabe am sozialen Leben erschwert wurde. Als Beispiele wurden die Einschränkung von physischen Aktivitäten oder Auslandsreisen genannt.

3.1.3 Genetische Test innerhalb der Familie

Einige Teilnehmende berichteten, dass ganze Familien gemeinsam den genetischen Test durchführen ließen, ohne zuvor ausführlich darüber gesprochen zu haben. Dies wurde unterschiedlich wahrgenommen: Teilweise bestand keine Erinnerung an individuelle Einwilligungen, teils erschwerte empfundener Gruppenzwang eigene Entscheidungen.

Eine Motivation zur gemeinsamen Testteilnahme war der Wunsch zu wissen, welches Familienmitglied Träger der Genvariante ist, um die betroffene Person unterstützen zu können. In der Annahme, dass das Testergebnis wenig bis gar keine negativen Konsequenzen mit sich brächte, sahen einige Teilnehmenden keinen Grund, den Test nicht gemeinsam zu machen. Andere Teilnehmende weigerten sich jedoch, den Test gemeinsam als Familie zu machen, oder wünschten, das Ergebnis selbst nicht zu erfahren. Betont wurde wiederholt, dass die Entscheidung zum Test jedem selbst überlassen werden sollte

3.1.4 Familienplanung

Die Teilnehmenden beschrieben Familienplanung als einen sehr relevanten, aber auch sehr schwierigen Aspekt des Lebens mit HCP. Einigkeit herrschte in dem Wunsch, ein gesundes Kind zu haben und in der Sorge, die Erkrankung weiter zu vererben. Vor allem die Teilnehmerinnen sprachen von Schuldgefühlen, die Krankheit an ihre Kinder vererbt zu haben.

Es wurden in diesem Zusammenhang drei Gründe genannt, die gegen ein Kind sprächen: die Sorge dem Kind einen Schaden zuzufügen, indem die Krankheit weitergegeben werde, ungefragt die Last der Erkrankung weiterzugeben, ohne dass die betroffene Person sich dafür entscheiden kann, und die Bedenken, dass die Sorgen um ein krankes Kind für die Familie zu groß sei, insbesondere für die Mutter.

Patient*innen und nicht erkrankte Familienmitglieder berichteten gleichermaßen, dass die Unsicherheit, ob sie die Erkrankung vererben würden, ein sehr belastender Aspekt der Familienplanung sei. Nicht zu wissen, ob das Kind erkranke, führte zu Stress und Ohnmachtsgefühlen. Auch bestand Unsicherheit, ob es angemessen sei, Kinder zu bekommen, wenn ein Elternteil selbst erkrankt sei und folglich nicht wisse, ob sie oder er sich langfristig um das Kind kümmern könnte.

Vereinzelt wurde aber auch von der Perspektive berichtet, dass die Erkrankung als nicht so belastend empfunden würde und damit die Entscheidung für ein Kind einfach sei. Ergänzend dazu wurde thematisiert, dass nicht sicher sei, ob das Kind die Erkrankung erben würde.

3.1.5 Weitere Ergebnisse der Interviewstudie

Neben Gentests wurden vier weitere Themen identifiziert und genauer untersucht: der unvorhersehbare Verlauf der Erkrankung HCP, HCP als erschütterndes Erlebnis, HCP als Teil des Alltags und auf HCP reduziert werden. Diese Ergebnisse werden in der Publikation „Lived Experience of Hereditary Chronic Pancreatitis – A Qualitative Interview Study“ ausführlich dargestellt (16).

3.2 Ergebnisse des systematischen Reviews

Im Folgenden wird auszugsweise auf die Ergebnisse des systematischen Reviews ethischer Aspekte eingegangen (18). Eine ausführlichere Darstellung der Ergebnisse ist in der Publikation Kruse et. al. nachzulesen. Die Suche in den elektronischen Datenbanken ergab insgesamt 307 Publikationen. Im ersten Schritt wurden davon durch ein Titel-Abstrakt Screening 135 Publikationen als potentiell relevant identifiziert. Im Folgenden wurden die Volltexte dieser Publikationen analysiert, dadurch wurden 38 Publikationen in das systematische Review eingeschlossen. Im Rahmen des Fußnotenscreenings der bereits eingeschlossenen Publikationen konnten zusätzlich 17 weitere Texte identifiziert und eingeschlossen werden. Somit bilden 55

Publikationen die Basis dieses Reviews, 54 davon sind in englischer Sprache verfasst und eine in Deutsch. Publiziert wurden sie zwischen 1988 und 2020.

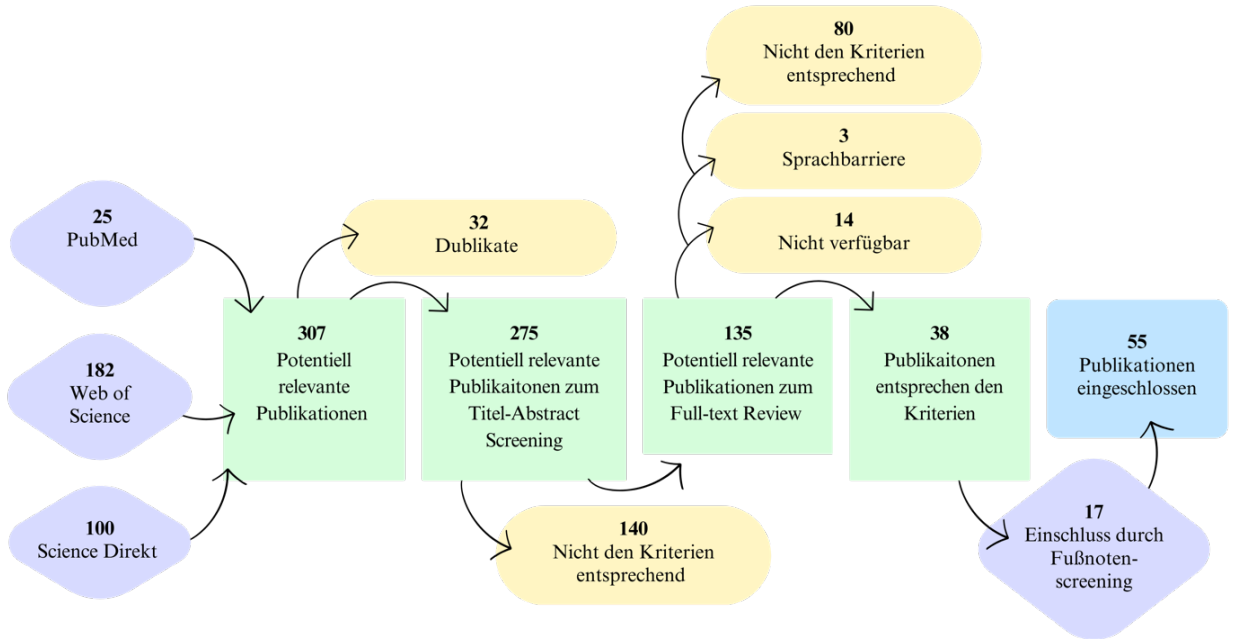

Abbildung 2 Flow Diagramm

Es konnten 918 relevante Textpassagen identifiziert und jeweils mit einem deskriptiven Code versehen werden. Diese Codes wurden zu 93 unterschiedlichen ethischen Aspekten zusammengefasst und den drei thematischen Hauptkategorien zugeordnet: Testprozess, Konsequenzen des Testergebnisses und kontextuelle Herausforderungen. Innerhalb dieser drei Kategorien wurden zur besseren Strukturierung 20 Unterkategorien aufgestellt:

1. Testprozedere: Ethische Aspekte, welche sich aus der Durchführung des genetischen Tests für seltenen Erkrankungen, aus der Analyse dieser Tests und der Mitteilung der Ergebnisse ergeben.
2. Konsequenzen des Testergebnisses: Ethische Aspekte, welche sich aus dem Wissen um das Testergebnis ergeben und den Reaktionen der Patient*innen auf diese Ergebnisse.
3. Kontextuelle Herausforderungen: Ethische Aspekte, die im Zusammenhang stehen mit den Umständen und Hintergründen der Tests, der Erkrankungen und den Testergebnissen.

3.2.1 Testprozedere

Diese Kategorie beinhaltet insgesamt 36 ethische Aspekte in neun Unterkategorien. Die ethischen Aspekte beziehen sich auf praktische Herausforderungen, welche in Situationen der direkten Arzt-Patient*innen Interaktion entstehen, wie das Einholen von informiertem Einverständnis oder die Interpretation der Testergebnisse.

Abbildung 3 Ergebnisse - Testprozedere

Ein besonders breit diskutierter ethischer Aspekt ist der Zugang zu genetischen Tests für seltene Erkrankungen, welcher eine Bandbreite von Themen beinhaltet. Dies beginnt mit der Überweisung zum Test, wozu es zunächst den Verdacht auf eine seltene Erkrankung genetischen Ursprungs bedarf (34,36,40). Eine besondere Herausforderung stellt dabei die geringe Anzahl lokaler Labore dar, welche einen adäquaten Test für die Diagnose einer seltenen Erkrankung anbieten (32,36,41–43). Zudem werden manche Tests nur im Rahmen von Studien angeboten, wodurch die Einholung der informierten Einwilligung erschwert wird und die Freiwilligkeit der Teilnahme an Forschungsvorhaben in Gefahr gerät (6,32,33,36,38,41,43–50).

Eine essentielle Komponente eines jeden genetischen Tests ist die professionelle Aufklärung und Beratung, um eine informierte Einwilligung einzuholen und eine adäquate Ergebnismitteilung zu gewährleisten (7,33–37,41,42,45,47,49,51–58). Vor dem Hintergrund des sich ständig und rapide weiterentwickelnden Feldes der genetischen Tests und der sehr spezifischen Eigenschaften der seltenen genetischen Erkrankungen stellt dies die Aufklärenden vor große Herausforderungen (7,33,38,44,45,49,59–63).

Eine Übersicht aller Unterkategorien und ethischen Aspekte der Kategorie Testprozedere ist der Abbildung 3 dargestellt.

3.2.2 Konsequenzen des Testergebnisses

Diese Kategorie umfasst 37 ethische Aspekte in sieben Unterkategorien und befasst sich mit Themen, welche direkt aus dem Testergebnis und den Umgang damit resultieren. Dazu gehören auch Reaktionen darauf.

Das Wissen um die möglichen Konsequenzen eines genetischen Tests ist relevant, um Patient*innen adäquat begleiten zu können. Einige dieser Konsequenzen wurden als positive Aspekte bewertet, wie zum Beispiel die Gewissheit um das Vorliegen der spezifischen Erkrankung (6,7,33,35,38,40,47,49,53,54,57,59,61,62,65–69). Daraus resultiert möglicherweise der Zugang zu einer Therapie (6,36,38,46,51,54,56,57,62,66,70,71).

In dem Falle, dass keine Behandlungsoptionen zur Verfügung stehen, stellt sich die Fragen, ob das reine Wissen um die Diagnose einen ausreichenden Grund für einen Test darstellt (43–45,49,58,70). Andererseits kann eine Diagnose auch bei fehlender Therapie positive Konsequenzen haben und zum Beispiel den Zugang zu Selbsthilfegruppen und den Kontakt über die sozialen Medien mit Individuen und Familien mit ähnlichen Diagnosen ermöglichen

(38,39,53,58,72). Dadurch kann ein Gemeinschaftssinn entstehen und die Unterstützung und der Austausch von Betroffenen wird ermöglicht.

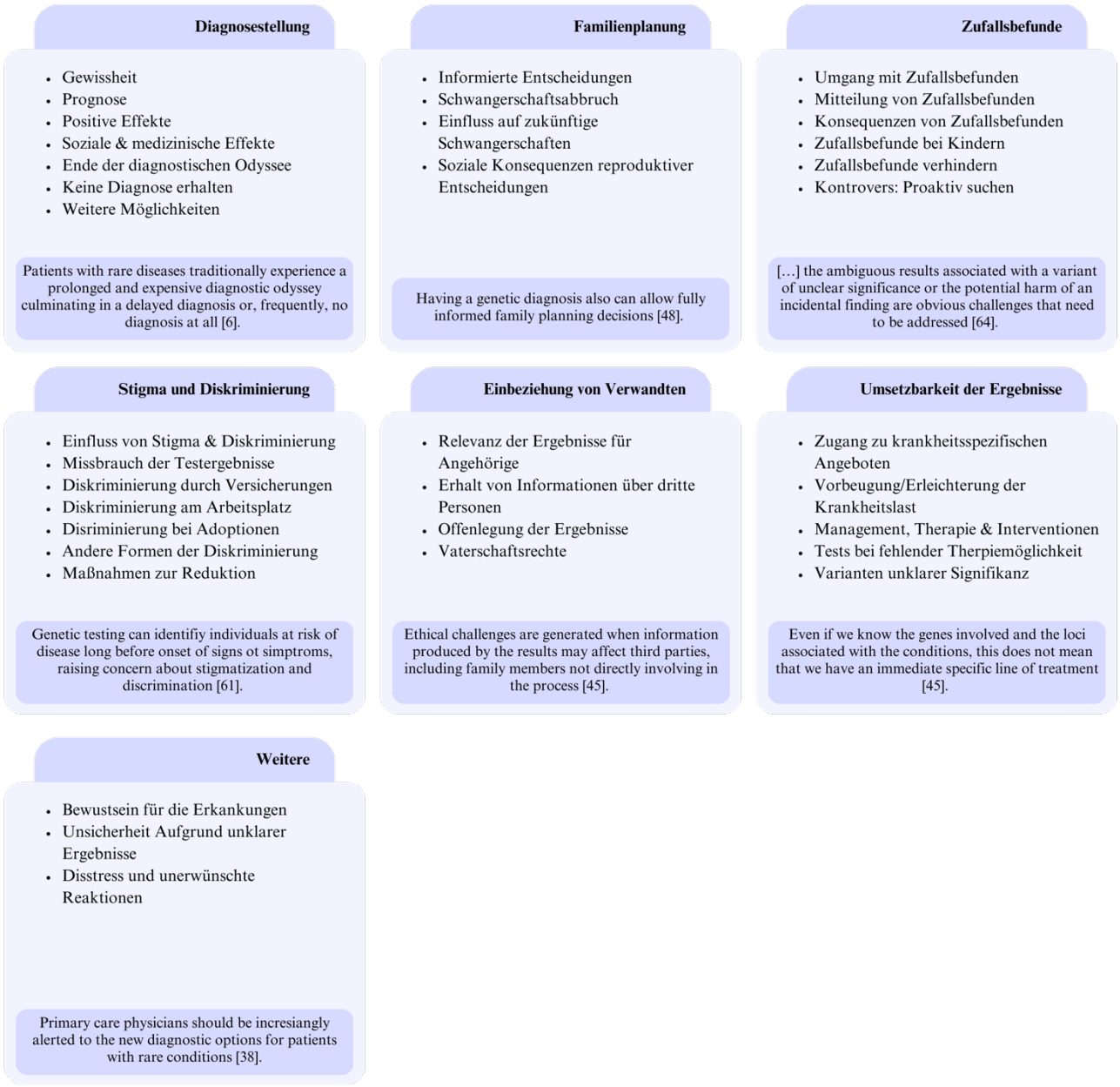

Abbildung 4 Ergebnisse - Konsequenzen des Testergebnis

Ein weiterer ethischer Aspekt ist die mögliche Relevanz der Testergebnisse für Personen, die nicht selbst getestet wurden. Durch die Bekanntgabe der Testergebnisse gegenüber Familienmitgliedern lernen diese für sie unter Umständen relevante, aber auch sehr private Informationen (45,49,51,65). Diese Informationen könnten für sie von großem Interesse und Nutzen sein, da sich daraus zum Beispiel Wahrscheinlichkeiten selber Träger*in der Mutation zu sein ableiten lassen (31,36,45,47–49,56,58,61,65,67,73,74). Unter Berücksichtigung der Interessen und

Rechte aller kann die Mitteilung und Einordnung dieser Befunde innerhalb der Familien eine große Herausforderung für die getestete Person darstellen (31,36,46,49,51,56,58,61,65,74).

3.2.3 Kontextuelle Herausforderungen

Diese Kategorie umfasst 21 ethische Aspekte in vier Unterkategorien. Diese Aspekte beziehen sich auf die sozialen und gesellschaftlichen Umstände genetischer Tests für seltene Erkrankungen. Die meisten dieser Aspekte liegen somit außerhalb der direkten Beeinflussbarkeit von Individuen, wie Ärzt*innen und genetischen Berater*innen, und beziehen sich mehr auf grundsätzliche Strukturen des Gesundheitswesens mit dessen Rahmenbedingungen.

Relevant erscheinen hier die verschiedenen ökonomischen Aspekte. Sie beeinflussen maßgeblich die Entwicklung und den Vertrieb von genetischen Tests für seltene Erkrankungen. Uneinigkeit herrscht in der wirtschaftlichen Bewertung dieser Tests. Sie werden einerseits als kosteneffizient beschrieben, da sie die diagnostische Odyssee deutlich verkürzen können und damit die Belastung der Betroffenen und des Gesundheitssystems reduzieren (6,37,39,53,54,66,70,76,77). Andererseits ist insbesondere die Entwicklung der einzelnen Tests sehr aufwendig und teuer, während sie entsprechend der Natur seltener Erkrankungen nicht häufig eingesetzt werden (37,50,52,65,68,74).

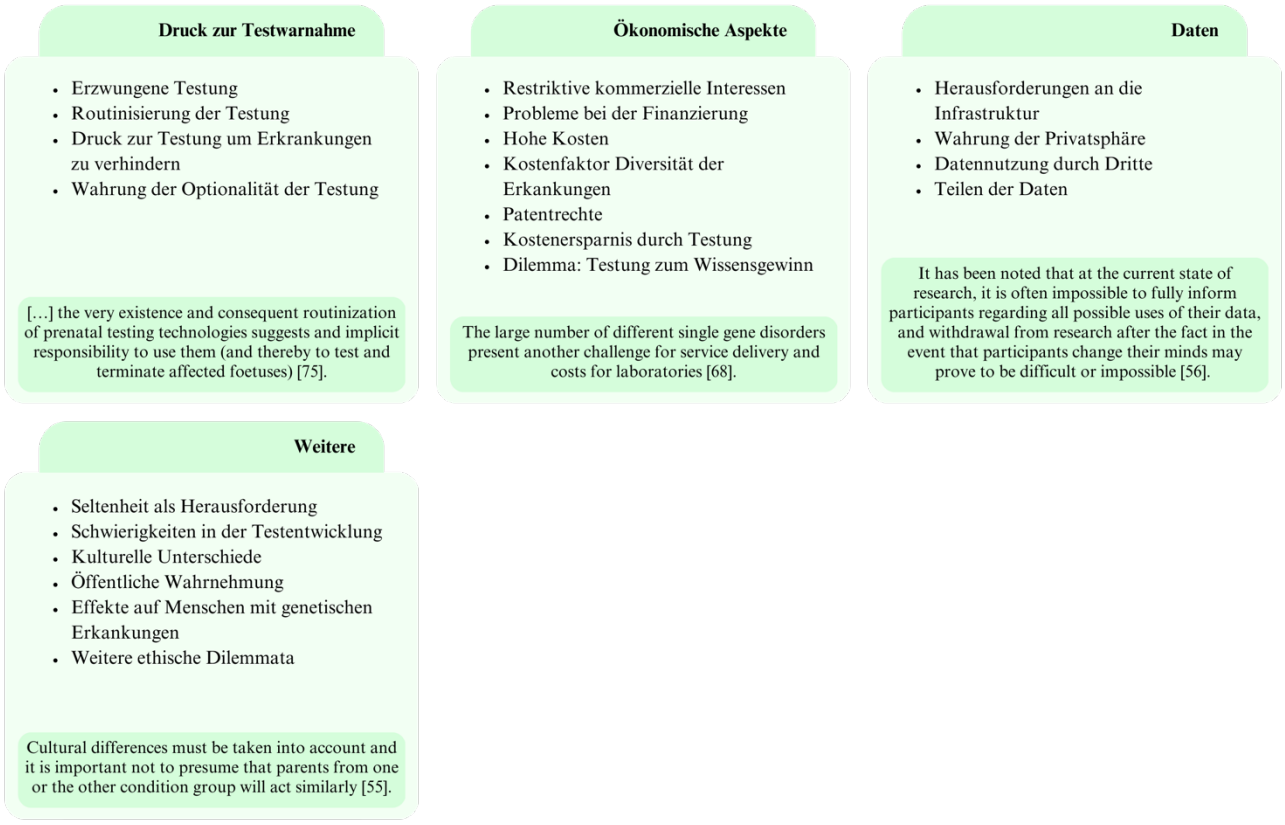

Abbildung 5 Ergebnisse - Kontextuelle Herausforderungen

Ein auch unter dem Aspekt der Wirtschaftlichkeit aufgegriffenes Thema ist die Frage nach Tests ohne direkte Konsequenzen, also zum Beispiel ein Test der zum reinen Informationsgewinn genutzt wird (68). Häufig ergeben sich aus der Diagnose einer seltenen Erkrankung keine therapeutischen Optionen, deren Inanspruchnahme als Nutzen betrachtet werden könnte. Bei genetischen Tests in der Schwangerschaft stellt sich nicht nur die Frage nach Therapien, sondern auch nach der möglichen Inanspruchnahme eines Schwangerschaftsabbruchs als konsequente Leidensvermeidung. Dies führt zu einer schwierigen Situation, da die Kosten-Nutzen Abwägung nicht eindeutig auf Seite des Nutzens liegt.

4. Diskussion

Die Interviewstudie zeigt, dass im Alltag der Betroffenen von HCP und ihren Angehörigen verschiedene Aspekte des Krankheitserlebens eine Rolle spielen. Herausfordernd ist insbesondere der Umgang mit genetischen Tests. Die Gründe für und gegen eine Testung sind vielfältig und individuell. Ähnliches gilt für die Wahrnehmung des Entscheidungsprozesses sowie der Testdurchführung und Ergebnismitteilung. Das systematische Review hat diese Erkenntnisse zu genetischen Tests bei HCP Patient*innen um Aspekte aus der Literatur zu seltenen Erkrankungen erweitert. Es konnte gezeigt werden, dass verschiedene Faktoren wie die Art der Erkrankungen, gesellschaftliche Ideale und Gegebenheiten der Gesundheitssysteme das Testerlebnis beeinflussen. Im Folgenden werden Ergebnisse der Interviewstudie und Fokusgruppe mit Aspekten des Reviews verglichen und diskutiert.

Im systematischen Review konnten genetische Tests in der Abwesenheit einer aussichtsreichen Therapie als ein zentrales ethisches Thema identifiziert werden (43–45,49,58,70). Dabei stellt sich die Frage, ob bei fehlender Option zur Leidensminderung durch eine Therapie, der Informationsgewinn durch das Wissen um die molekulare Diagnose den mit einer genetischen Testung verbundenen Aufwand rechtfertigt. Ein Beispiel für solch eine Situation stellt die HCP da. Für HCP gibt es keine Heilung. Es besteht nur die Möglichkeit einer symptomatischen Therapie (78,79). In den Einzelinterviews und der Fokusgruppe wurde klar, dass eine molekulare Diagnose viel Sicherheit bietet. Zum einen können andere, möglicherweise heilbare Erkrankungen, ausgeschlossen werden, zum anderen kann eine frühzeitige Patient*innenedukation beginnen. Dies ermöglicht auch eine frühe Inanspruchnahme unterstützender Angebote wie die Vernetzung in Selbsthilfegruppen. Auch die nicht erkrankten Angehörigen profitieren von der sicheren Diagnose. Dadurch können sie eine individuelle Versorgung und Unterstützung der Erkrankten sicherstellen. Dieses Ergebnis deckt sich mit dem des systematischen Reviews. Einer

der Vorteile einer molekularen Diagnose auch ohne spezifische Therapie wurde in der Gewissheit um die Erkrankung gesehen (7,33,35,38,39,47,49,53,54,57,59,61,65–69). Damit einher gehen häufig auch krankheitsspezifische Informationen wie eine Prognose mit zu erwartenden Symptomen und möglicherweise auch eine Lebenserwartung (6,7,33,35,38–40,46,47,49,53, 54,57,59,61,62,65–69,77). Des Weiteren ermöglicht dieses Wissen den Zugang zu krankheitsspezifischen Therapie- und Begleitungsangeboten (38,39,53,58,72). Eine ergänzende Perspektive der Interviewstudie ist, dass dieses Wissen den Betroffenen und Angehörigen auch bei Erkrankungen mit schlechter Vorhersehbarkeit ermöglicht, Vorbereitungen für den nächsten Schub zu treffen. Zusätzlich ermöglicht eine definitive Diagnose auch den Zugang zu sozialen Leistungen und Unterstützungsangeboten (6).

Ein Zeitpunkt, welcher durch die Interviewteilnehmenden als besonders relevant identifiziert wurde und auch in der Fokusgruppe genauerer Untersuchung zukam, ist die Familienplanung. In den Publikationen des systematischen Reviews wird die genetische Diagnose als Schlüssel zu einer informierten Familienplanung angesehen (6,38–40,47,48,51,60,66,70,71,75). In der Interviewstudie wurde darüber hinaus nicht nur das Ergebnis eines genetischen Tests, sondern auch das subjektive Krankheitsempfinden als Entscheidungsgrundlage der Familienplanung genannt. Dabei spielt nicht nur die potentielle Erkrankung des Kindes eine Rolle, sondern auch die Frage nach dem erkrankten Elternteil und in wie weit eine Versorgung des Kindes, ob erkrankt oder nicht, gewährleistet werden kann. Damit werden Nuancen abgebildet, die im systematischen Review nicht vorkommen. Was die meisten Teilnehmenden der Interviews eint, ist der Wunsch, ein möglichst gesundes Kind zu bekommen und dem Kind nicht durch die Vererbung einer Erkrankung zu schaden. Dieser Aspekt wird auch in der Literatur gefunden. Weiterführend wird dort besonders intensiv der Schwangerschaftsabbruch als Konsequenz einer pränatalen Diagnose als Mittel diskutiert, einen möglichen Schaden beim Kind zu verhindern (7,40,46,47,52,55,60,66,68,69,74–77,80).

Ist ein Kind ohne Pränataldiagnostik geboren und eine seltene genetische Erkrankung in der Familie bekannt, stellt sich die Frage nach dem idealen Zeitpunkt zur Durchführung eines genetischen Tests. Die Teilnehmenden der Interviewstudie betonten, dass die Inanspruchnahme eines genetischen Tests eine sehr individuelle Entscheidung sei und von verschiedenen, auch äußeren Faktoren abhänge. Daher konnten keine pauschale Aussage bezüglich des idealen Zeitpunktes zur genetischen Testung getroffen werden kann. Als einzigen Zeitpunkt eindeutig abgelehnt wurde eine Testung auf HCP direkt nach der Geburt. Im systematischen Review wird diese Thematik differenzierter und im Kontext verschiedener Erkrankungen betrachtet. Dabei

wird zum einen nach dem Anlass zur Testung unterschieden, ob es sich um eine präsymptomatische Testung bei familiärer Prädisposition oder anderen Risikofaktoren handelt, oder um das Testen bereits symptomatischer Individuen (46,59,81). Zum anderem ist die Art der Erkrankung an sich relevant, vor allem der zu erwartende Zeitpunkt des Eintretens der Symptome (35,37,81–83). Auch aus dem systematischen Review kann kein eindeutiger Konsens bezüglich eines optimalen Zeitrahmens zur genetischen Testung abgeleitet werden. Eine Testung in der Kindheit wird insgesamt kritisch betrachtet (7,35,49,73). Die Teilnehmenden der Interviewstudie berichten von einer überraschend unterschiedlichen Wahrnehmung einer genetischen Testung in der eigenen Kindheit. Teilweise wird sich gut an den genetischen Test und die Ergebnismitteilung erinnert, bei anderen Teilnehmenden ist jedoch überhaupt keine Erinnerung vorhanden. Dies überrascht dahingehend, dass insbesondere ein positives genetisches Testergebnis potentiell eine identitätsstiftende Wirkung haben und das weitere Leben bedeutsam beeinflussen kann. Dies gilt sowohl im Kontext einer gezielteren Inanspruchnahme von Gesundheitsdienstleistungen wie auch in einer veränderten Familiendynamik. Möglicherweise kann ein besonderes Zusammengehörigkeitsgefühl mit anderen (betroffenen) Familienangehörigen entstehen, geeint durch das gemeinsame Erleben einer seltenen genetischen Erkrankung.

Dieses Zusammengehörigkeitsgefühl innerhalb einer Familie beeinflusst auch die Entscheidung zur Durchführung eines genetischen Tests. Die Interviewstudie ergab, dass die Entscheidung zur Inanspruchnahme genetischer Testangebote oft gemeinsam mit der Familie getroffen wurde. Im Kontrast dazu wurde in dem systematischen Review kein einziger Aspekt zur Relevanz von Familiendynamiken in der Inanspruchnahme von Testangeboten gefunden. In den Ergebnissen fallen lediglich relevante ethische Aspekte der Ergebnisbewertung auf. Dazu gehört zum Beispiel der Umgang mit den Testergebnissen. Diese Ergebnisse können eine große persönliche Relevanz für die Angehörigen haben (31,36,45,47–49,56,58,61,65,67,73,74). In diesem Rahmen ergeben sich Problemfelder wie informierte Einwilligung, welche nicht von Angehörigen für das individuelle Testergebnis eines Familienmitgliedes gegeben werden kann (49). Zusätzlich wird die Privatsphäre der Angehörigen gefährdet, wenn die erkrankte Person Informationen erfährt, die sich von ihr selbst auf die Familienangehörige übertragen lässt. Andererseits wird auch die Frage nach dem Zurückhalten von Ergebnissen, die eine Relevanz für die Angehörigen haben könnten, und dessen mögliche Folgen diskutiert (36,45,56). Weiterführend wird in der Interviewstudie von einzelnen Teilnehmenden von einem Druck zur Testung durch die Angehörigen berichtet. Auch das systematische Review benennt Druck zur Inanspruchnahme genetischer Testangebote als einen wichtigen ethischen Aspekt (36,52,55,58,68). Aber auch in diesem Fall wird in keiner der Publikationen des systematischen Reviews der

Druck durch Familienangehörige thematisiert. Es wird diskutiert, dass die Routinisierung der Testangebote und die zunehmende Verfügbarkeit einen indirekten Druck ausüben, diese auch in Anspruch zu nehmen sowie ein unter Umständen offensichtlicher Druck durch außenstehende Instanzen wie zum Beispiel Ärzt*innen oder ganz allgemein die Gesellschaft (36,49,52, 55,69,75). Dies bringt die für einen genetischen Test aufklärenden Personen in herausfordernde Situationen. Zum einen muss sichergestellt werden, dass jede einzelne Person den Test freiwillig durchführen lässt, insbesondere wenn ganze Familien gemeinsam das Testangebot wahrnehmen. Auch muss die Voraussetzung erfüllt sein, dass jedes Familienmitglied entsprechend aufgeklärt wurde. Andererseits muss sichergestellt werden, dass die Testergebnisse und deren Relevanz für die Patient*innen persönlich und die nicht getesteten Angehörigen ausführlich besprochen werden. Auch sollten Strategien erarbeitet werden, um entsprechende Gespräche über einen anstehenden Test und im Verlauf die erhaltenden Testergebnisse innerhalb der Familie konfliktfrei führen zu können. Mögliche Herausforderungen und Konflikte sollten im Vorhinein erörtert werden, um adäquate Lösungsansätze zu finden.

5. Fazit

Diese Arbeit zeigt sehr deutlich, dass mit der genetischen Testung für seltene Erkrankungen komplexe ethische Herausforderungen einhergehen. Die bisherige Literatur vernachlässigt insbesondere die Perspektive der Angehörigen. Es konnte jedoch gezeigt werden, dass die Berücksichtigung dieser Perspektiven im direkten Umgang mit Betroffenen von großer Bedeutung ist. Mögliche Interessen und Reaktionen können besser antizipiert werden. Dynamiken können besser verstanden werden, die Motivationen zur Durchführung genetischer Testangebote beeinflussen. Bei einer genetischen Beratung sollte insbesondere der Gemeinschaftsaspekt der Familie berücksichtigt werden. Um eine adäquate Versorgung aller von einer Erkrankung betroffener Personen zu ermöglichen, sollte über die Perspektive der direkt betroffenen Patient*innen hinausgedacht werden. Eine mögliche Relevanz der Testergebnisse einer Einzelperson für deren Angehörige muss antizipiert werden. Gleichzeitig muss die freiwillige Teilnahme einer jeden Person sichergestellt werden und die Privatsphäre der direkt am Test beteiligten wie auch unbeteiligten Angehörigen bestmöglich gewahrt werden. Somit erfordert der Umgang mit genetischen Tests für seltene Erkrankungen eine besondere Sensibilität. In der Literatur zeigt sich hier eine Lücke. Der Einfluss des individuellen Krankheitserleben sowie der Familiendynamik auf die Annahme von Testangeboten sowie dem Umgang mit Ergebnissen muss für weitere, seltene genetischer Erkrankungen untersucht werden. Das Ziel sollte sein, die bestmögliche Patient*innenversorgung sicher zu stellen.

IV. Anhang

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b. Interviewleitfäden

PePPP „Ethische Aspekte bei hereditärer chronischer Pankreatitis: Eine qualitative Interviewstudie“ (Patient*innen)

Einstieg	
Lieber Herr/liebe Frau […], schön, dass Sie sich bereit erklärt haben, das Interview mit mir zu führen.	Hinführung
Bevor wir beginnen, möchte ich kurz etwas über den Gesprächsablauf sagen. Damit ich mich besser auf das Gespräch konzentrieren kann, würd ich das Gespräch gerne aufzeichnen. **Sind sie damit einverstanden?** [TeilnehmerIn einverstanden → Tonband einschalten, falls nicht → Notizen machen]	Tonbandgerät
So, das Tonbandgerät läuft nun. Wir hatten ja eben schon darüber gesprochen, dass Ihre Teilnahme an diesem Forschungsprojekt freiwillig ist. Sie können das Interview selbstverständlich jederzeit ab- oder unterbrechen. Ansonsten können Sie im Gespräch gerne so ausführlich erzählen, wie Sie möchten – wir haben Zeit.	Freiwilligkeit Unterbrechungen Ermunterung
Haben Sie noch Fragen zum Gesprächsablauf?	Nachfragen
Wir wollen heute über Ihre Krankheit, die chronische Pankreatitis sprechen, wie haben Sie denn überhaupt gemerkt, dass Sie diese Erkrankung haben?	Einstiegsfrage

Themenkomplex I: Patientenbiographie	
Die Diagnose hat ja oft eine lange Vorgeschichte, können Sie mir darüber etwas erzählen? Woran haben Sie denn gemerkt, dass Sie erkrankt sind? Wie/Wann haben Sie erfahren, dass Sie Pankreatitis haben? Hat sich etwas verändert, dadurch dass die Diagnose nun auf dem Tisch lag?	Weg zur Diagnose Schwierigkeiten
Wie ging es dann weiter? Wie ist es denn, mit der Krankheit zu leben? (Wechselphasen zw. krank und gesund?) Wie geht es Ihnen mit der Krankheit momentan?	Leben mit der Erkrankung
Haben Sie Einschränkungen im Alltag? Welche Folgen hat/hatte die Krankheit auf Ihre Ausbildung? Welche Auswirkungen gibt es auf den Beruf? [falls zutreffend] Hat die Krankheit Auswirkungen auf das Familienleben?	Ausbildung/Beruf Familienplanung
Können Sie bitte den folgenden Satz vervollständigen: Leben mit chronischer Pankreatitis bedeutet für mich…	

Themenkomplex II: Genetik	
Wir haben ja bereits darüber gesprochen, dass es ein langer Weg zur Diagnose sein kann. Es gibt ja auch die Möglichkeit, sich daraufhin testen zu lassen, ob man die Veranlagung für chronische Pankreatitis trägt. Haben Sie sich eigentlich genetisch untersuchen lassen?	Gründe
Ja/Nein → Können Sie mir erzählen, wie es zu dieser Entscheidung kam? Können Sie beschreiben, wie Sie das entschieden haben? Versetzen Sie sich doch noch mal in die Situation. Wie war das? Würden Sie heute anders entscheiden?	Entscheidungs-Prozess
Gab es vor dem Test eine Beratung? Wenn ja, wie haben Sie diese empfunden? Haben Sie in die Entscheidung andere Personen miteinbezogen?	Beratung Familie
Bei Testung: Wie ging es nach der Testung weiter? Was haben Sie mit den Informationen gemacht? Haben Sie diese Informationen eigentlich auch mit anderen Personen geteilt? Wie haben diese reagiert?	Umgang mit den Informationen

Hat sich durch die Informationen in Ihrem Leben etwas geändert? Was hat das gemacht? Haben Sie ein Beispiel dafür? (Familienplanung) Wir haben bisher viel über die chronische Pankreatitis gesprochen, spielt das Thema „Krebs“ in Ihrem Leben auch eine Rolle? Was geht Ihnen bei dem Thema „Krebs“ durch den Kopf? Wie gehen Sie mit diesem Thema um?	Einfluss der Informationen Krebsrisiko

Themenkomplex III: Patientenselbsthilfegruppen	
Den Kontakt zu Ihnen haben wir ja über den „Verein Deutsche Pankreashilfe“ aufgenommen. Wie kam es eigentlich dazu, dass Sie Mitglied in diesem Verein wurden?/ Wie kam es dazu, dass Sie in Kontakt mit diesem Verein gekommen sind?	Gründe
Können Sie mir als Außenstehende erzählen, was diese Gruppe leistet? Über was reden Sie in der Gruppe? Wen laden Sie ein? Wie helfen sie sich? Gibt es sonst noch etwas?	Funktion
Können Sie an einem Beispiel beschreiben, wie Sie durch den Verein Hilfe/Unterstützung erhalten? Fehlt Ihnen dabei vielleicht etwas? Wünschen Sie sich als Patient/in mehr Unterstützung, zum Beispiel durch Ihre Ärztin?	Unterstützung

Themenkomplex IV: Beteiligung an Forschung	
Ich würde mit Ihnen gerne noch über das Thema „medizinische Forschung“ sprechen Haben Sie schon mal an einer medizinischen Studie teilgenommen?	Erfahrungen Forschung
Ja: Können Sie mir erzählen, wie es dazu kam? Warum haben Sie bei der Studie mitgemacht? (Was für eine Studie? Was haben Sie gemacht? Haben Sie die Ergebnisse erfahren?)	Gründe Motivation
Nein → zwei Möglichkeiten: Patient hatte noch nicht die Möglichkeit, sich an Studien zu beteiligen oder Patient hat sich gegen eine Teilnahme entschieden.	
Stellen Sie sich einmal vor, die medizinische Forschung hätte genügend Geld und die technischen Möglichkeiten, alles zu erforschen, was Sie sich wünschen würden. Was würden Sie sich wünschen, soll in Bezug auf Ihre Erkrankung erforscht werden?	Wünsche

Offener Ausstieg
Möchten Sie noch etwas erzählen, was ich vergessen habe? Gibt es noch etwas, was Sie ergänzen möchten?
Sozialdemographie → Checkliste
Ich hätte nun noch ein paar konkrete Fragen an Sie…

Danke sagen!

PePPP „Ethische Aspekte bei hereditärer chronischer Pankreatitis: Eine qualitative Interviewstudie“ (Angehörige)

Einstieg	
Lieber Herr/liebe Frau […], schön, dass Sie sich bereit erklärt haben, das Interview mit mir zu führen.	Hinführung
Bevor wir beginnen, möchte ich kurz etwas über den Gesprächsablauf sagen. Damit ich mich besser auf das Gespräch konzentrieren kann, würd ich das Gespräch gerne aufzeichnen. **Sind sie damit einverstanden?** [TeilnehmerIn einverstanden → Tonband einschalten, falls nicht → Notizen machen]	Tonbandgerät
So, das Tonbandgerät läuft nun. Wir hatten ja eben schon darüber gesprochen, dass Ihre Teilnahme an diesem Forschungsprojekt freiwillig ist. Sie können das Interview selbstverständlich jederzeit ab- oder unterbrechen. Ansonsten können Sie im Gespräch gerne so ausführlich erzählen, wie Sie möchten – wir haben Zeit.	Freiwilligkeit Unterbrechungen Ermunterung
Haben Sie noch Fragen zum Gesprächsablauf?	Nachfragen
Wir wollen heute über die „chronische Pankreatitis“ sprechen. **Was wissen Sie eigentlich zu dieser Erkrankung?**	Einstiegsfrage

Themenkomplex I: Patientenbiographie/Situation der Angehörigen	
Die Diagnose hat ja oft eine lange Vorgeschichte, haben Sie den Weg Ihres Mannes / Ihrer Frau / Ihres Lebenspartners / … miterlebt? Wie/Wann haben Sie erfahren, dass Ihr Angehöriger Pankreatitis hat?	Weg zur Diagnose Schwierigkeiten
Wie ging es dann weiter?	
Wie ist es denn, mit jemandem zu leben, der diese Krankheit hat? (Wechselphasen zw. krank und gesund?) Wirkt sich die Erkrankung auch auf Ihr Leben aus? Wenn ja, können Sie ein Beispiel dafür schildern?	Leben mit einem erkrankten Angehörigen
Beeinträchtigt die Krankheit Ihres Angehörigen Ihren gemeinsamen Alltag? *Welche Folgen hat/hatte die Krankheit auf Ihre Ausbildung?* *Welche Auswirkungen gibt es auf den Beruf? [falls zutreffend]* Hat die Krankheit Auswirkungen auf das Familienleben?	Ausbildung/Beruf Familienplanung
Können Sie bitte den folgenden Satz vervollständigen: Mit jemanden zu leben, der chronische Pankreatitis hat, bedeutet…	

Themenkomplex II: Genetik	
Es gibt ja auch die Möglichkeit, sich daraufhin testen zu lassen, ob man die Veranlagung für chronische Pankreatitis trägt. Hat sich Ihr Angehöriger eigentlich genetisch untersuchen lassen?	Gründe
Ja/Nein → Waren Sie in diese Entscheidung eingebunden? Versetzen Sie sich doch noch mal in die Situation. Wie war das? Würden Sie sich in der Situation Ihres Angehörigen anders entscheiden?	Entscheidungs-Prozess
Gab es eine Beratung vor dem Test? Wenn ja, wie haben Sie diese empfunden? Wurden in die Entscheidung noch andere Personen miteinbezogen?	Beratung Familie
Bei Testung: Wie ging es nach der Testung weiter?	Umgang mit den Informationen

Hat ihr Angehöriger die Informationen mit Ihnen geteilt? Wie haben Sie reagiert? Hat sich durch die Informationen in Ihrem Leben etwas geändert? Was hat das gemacht? Haben Sie ein Beispiel dafür? (Familienplanung)	Einfluss der Informationen
Wir haben bisher viel über die chronische Pankreatitis gesprochen, spielt das Thema „Krebs“ in Ihrem Familienleben/in Ihrer Partnerschaft auch eine Rolle? Was geht Ihnen bei dem Thema „Krebs“ durch den Kopf? Wie gehen Sie mit diesem Thema um?	Krebsrisiko

Themenkomplex III: Patientenselbsthilfegruppen	
Den Kontakt zu Ihnen haben wir ja über den „Verein Deutsche Pankreashilfe“ aufgenommen. Wie kam es eigentlich dazu, dass Sie in Kontakt zu diesem Verein gekommen sind?	Gründe
Können Sie mir als Außenstehende erzählen, was diese Gruppe leistet? Gibt es sonst noch etwas?	Funktion
Können Sie an einem Beispiel beschreiben, wie Sie durch den Verein Hilfe/Unterstützung erhalten? Fehlt Ihnen dabei vielleicht etwas? Wünschen Sie sich mehr Unterstützung, zum Beispiel durch Ärzte?	Unterstützung

Themenkomplex IV: Beteiligung an Forschung	
Ich würde mit Ihnen gerne noch über das Thema „medizinische Forschung“ sprechen Hat Ihr Mann / Ihre Frau schon mal an einer (anderen) Studie teilgenommen?	Erfahrungen Forschung
Ja: Können Sie mir erzählen, wie es dazu kam? Warum hat ihr Mann / ihre Frau an der Studie teilgenommen? (Was haben Sie gemacht? Haben Sie die Ergebnisse erfahren?)	Gründe Motivation
Nein → zwei Möglichkeiten: Patient hatte noch nicht die Möglichkeit, sich an Studien zu beteiligen oder Patient hat sich gegen eine Teilnahme entschieden.	
Stellen Sie sich einmal vor, die medizinische Forschung hätte genügend Geld und die technischen Möglichkeiten, alles zu erforschen, was Sie sich wünschen würden. Was würden Sie sich wünschen, was soll hinsichtlich der „chronischen Pankreatitis“ erforscht werden?	Wünsche

Offener Ausstieg
Möchten Sie noch etwas erzählen, was ich vergessen habe? Gibt es noch etwas, was Sie ergänzen möchten?

Sozialdemographie → Checkliste: Ich hätte nun noch ein paar konkrete Fragen an Sie…

Danke sagen!

c. Stellungsnahmen der Ethikkommission

EINGANG 07. JUNI 2017

Universitätsmedizin
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Ethikkommission

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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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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*
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Lars Kaltheuner, Medizinstudent	*Katrin Packhäuser, Medizinstudentin**

*bei der Sitzung am 30.05.2017 anwesend

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BEARBEITER
Frau Dr. K. Saljé

DATUM
30.04.2018

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

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

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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:

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

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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 (≥2 individuals with pancreatitis in ≥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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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

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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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SYSTEMATIC REVIEW
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Genetic Testing for Rare Diseases: A Systematic Review of Ethical Aspects

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Genetic testing is associated with many ethical challenges on the individual, organizational and macro level of health care systems. The provision of genetic testing for rare diseases in particular requires a full understanding of the complexity and multiplicity of related ethical aspects. This systematic review presents a detailed overview of ethical aspects relevant to genetic testing for rare diseases as discussed in the literature. The electronic databases Pubmed, Science Direct and Web of Science were searched, resulting in 55 relevant publications. From the latter, a total of 93 different ethical aspects were identified. These ethical aspects were structured into three main categories (process of testing, consequences of the test outcome and contextual challenges) and 20 subcategories highlighting the diversity and complexity of ethical aspects relevant to genetic testing for rare diseases. This review can serve as a starting point for the further in-depth investigation of particular ethical issues, the education of healthcare professionals regarding this matter and for informing international policy development on genetic testing for rare diseases.

Keywords: genetic testing, rare diseases, orphan diseases, genetic counselling, ethics

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INTRODUCTION

Around 29 million people in the European Union (EU) (European Union, 2008), 30 million people in the Unites States of America (USA) (Global Genes, 2020) and around 400 million people worldwide are affected by one out of 5,000 to 8,000 different rare diseases (Global Genes, 2020). There is no uniform definition of rare diseases. A disease is considered as rare in the EU if it affects no more than 5 in 10,000 people (European Union, 2008), this definition will be adhered to in the following article. Half of the patients diagnosed with a rare disease are children and approximately 3% of newborns are affected by a rare disease (Global Genes, 2020; Eurordis, 2005). At least 80% of rare diseases have a genetic origin (Global Genes, 2020). This can mean either the involvement of one or several genes or chromosomal abnormalities. Often entire families or ethnic groups are affected due to the hereditary nature of the disease. However, rare diseases can be caused by *de novo* mutations affecting single individuals (Eurordis, 2005). Genetic and phenotypic variability add to the incomplete knowledge of rare diseases which complicates the process of diagnosis, leading to a diagnostic odyssey lasting an average of 8 years (Global Genes, 2020, Wright et al., 2018). This not only poses an immense strain and psychological distress on the patients and their families but also presents a serious challenge and burden to healthcare systems (Wright et al., 2018).

A precise molecular diagnosis is essential for the efficient handling of rare diseases in order to provide disease management and treatment options. In addition, it enables informed future

family planning decisions and the formation of supportive networks of individuals and families affected by rare diseases (European Union, 2008; Wright et al., 2018). Early and precise diagnoses help to reduce further invasive and expensive testing and the psychological stress associated with an unknown diagnosis (Liu et al., 2019; Soden et al., 2012). A genetic diagnosis might not only be of interest for symptomatic individuals but can also be beneficial as a screening procedure in the identification of carriers and asymptomatic individuals and, thus, contributes to the secondary prevention of both benign and malignant diseases (Pulst, 2000).

Advances in genetic testing, especially next generation sequencing technologies (NGS), have positively impacted the likelihood of obtaining a genetic diagnosis in a timely manner (Wright et al., 2018; Liu et al., 2019, Soden et al., 2012). However, genetic testing still requires proper counseling prior to testing in order to obtain informed consent, and after the test when the results are delivered (Soden et al., 2012; Liu et al., 2019). If not properly understood by the patient, the disclosure of genetic test results might lead to adverse reactions, such as heightened anxiety and unnecessary precautionary measures (Committee on Bioethics, 2001). A positive test result in an individual might also provide genetic information about relatives who have not given their direct consent to this information. This can lead to communication challenges and brings the medical professional disclosing the information and the receiving patient into an uncomfortable position (Pulst, 2000; Ellis et al., 2001; Gross, 2002).

The rapid technological advancements in genetics and the lack of education in this field limit the ability of many nonspecialized physicians to partake in the much needed professional discussion of ethical issues in genetic testing (Pulst, 2000). The widespread lack of experience with rare diseases often only intensifies this problem. Issues of particular relevance for rare diseases include the ethical justification of testing for a condition that does not have treatment options available, which is the case for many rare diseases, or the seemingly ubiquitous risk of receiving a result of unknown or ambivalent significance and the necessary measures to follow (Boycott et al., 2013; Warman Chardon et al., 2015; Petrikin et al., 2015). Less obvious issues also need thorough ethical discussion, such as counseling for postmortem genetic testing, which is most relevant in instances of sudden unexpected deaths (Working Group commissioned by the Ontario Genetic Testing Advisory Committee, 2016; Tester and Ackermann, 2017). Additionally, accessibility of genetic testing itself can bear ethical challenges when routine care laboratories do not provide the tests and research settings remain the only option. Laboratories often lack any interest in providing genetic testing, especially for extremely rare diseases, since these tests have a low volume and the development and validation can be expensive (Ledbetter and Faucett, 2008).

This review is the first, to the best of the authors' knowledge, to present a profound overview of all ethical aspects of genetic testing for rare diseases as published in the literature. In systematizing ethical problems related to this field this review can assist researches in the field of genetics as well as clinicians and counsellors in enhancing the moral sensibility for issues pertinent to their professional practice. For example, this review systematically gives a list of ethical issues occurring at the micro-level of patient-provider-contact and enables a further in-depth literature analysis of moral problems relevant for the individual reader. It furthermore provides a systematic basis for the ethical education of not only healthcare professionals but also patients, their families and other relevant stakeholders. This review provides a systematic background for further empirical and normative investigations of ethical aspects and is meant as a comprehensive aid to health policy making.

MATERIALS & METHODS

Aim

This article provides an overview of the full spectrum of ethical aspects in genetic testing for rare diseases based on a systematic review of the literature closely following the methodology used by Strech et al. (Strech et al., 2013). The reporting is in line with the PRISMA statement. The review does not aim to answer a specific normative-ethical question, but covers several ethical aspects related to genetic testing for rare diseases. The ethical aspects are qualitatively extracted from the publications and presented in a descriptive manner.

Search Methods

The electronic databases Pubmed, Science Direct and Web of Science were searched (see **Figure 1** for search strings and flow diagram). The results of each search were downloaded and duplicates discarded. The database searches were conducted in June 2020. Language restrictions for the search were English and German.

Eligibility Criteria

The only eligibility criterion for a publication to be included in the current systematic review was the description of an ethical aspect related to genetic testing for rare diseases.

"Rare diseases" are defined according to the EU as a disease affecting no more than 5 in 10,000 people (living in the EU) (European Union, 2008). Publications discussing rare diseases as a general topic were included as well as publications focusing on specific groups of rare diseases (e.g., neuromuscular disorders) or a single rare disease (e.g., Gaucher's disease). Publications dealing exclusively with genetic screening, for example, newborn screening, were not included since this review focuses on predictive genetic testing rather than on population screening.

"Ethical aspects" were identified on the basis of the ethical theory of principlism, according to Beauchamp and Childress (Beauchamp & Childress, 2019). This approach defines four ethical principles: Respect for autonomy, non-maleficence, beneficence and justice. These four principles provide a general orientation and ought to be followed unless they conflict. If a conflict arises and not all principles can be followed, the conflicting principles need to be balanced in

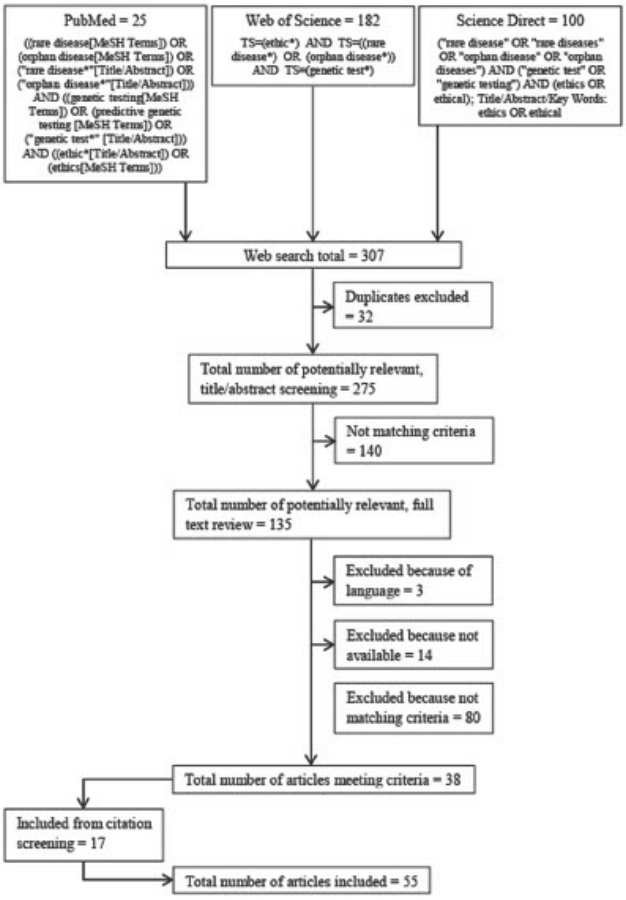

FIGURE 1 | Flow diagram and search strings.

order to reach a solution. This act of balancing is always performed in the light of the specific situation.

"Genetic testing" is defined as an laboratory examination aimed at detecting or ruling out the presence of hereditary illnesses or predisposition to such conditions in a person by directly or indirectly analyzing their genetic heritage (e.g., genes, chromosomes, proteins) (European Union, 1997).

Up until the completion of this article, no definite set of criteria had been established on how to conduct a quality appraisal for reviews of ethical literature (Mertz, 2019). Consequently, no quality appraisal was conducted in the present review. An inadequate quality appraisal might withhold valuable features because the intention of this review is to display the full spectrum of ethical aspects.

No restriction was applied to the type of publications included in this review. Therefore, not only original articles but also comments, editorials and book chapters were included. In order to display the full spectrum of ethical aspects relevant to the review question, not only argument-based but also empirical literature (when discussing ethical arguments) was included (See **Figure 2** for publication types).

Similarly, no limit was established regarding the year of publication in order to include all ethical aspects mentioned and portray changes in the discussion over time.

Study Selection

A title/abstract screening was performed on all publications retrieved from the databases searched. If publications appeared

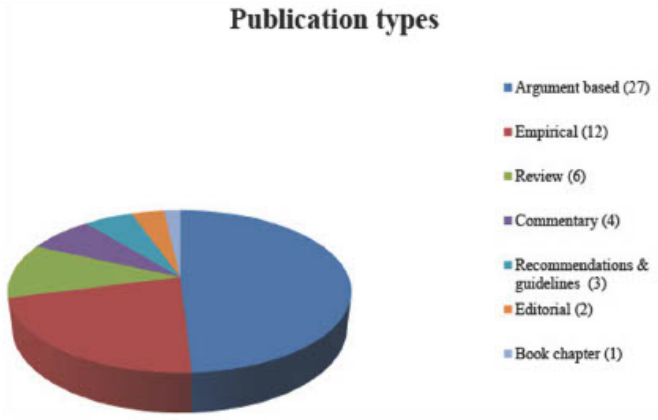

FIGURE 2 | Publication types.

to meet the eligibility criteria, in a second step, the full text was analyzed. If a publication still met the criteria, i.e., addressed ethical aspects in the context of genetic testing for rare diseases, it was included in this review. After the inclusion of publications derived from the database search, an additional screening of all references and footnotes was conducted and supplementary publications were included based on the criteria described (see **Figure 1** for search strings and flow diagram).

Extraction and Synthesis of Ethical Aspects

The data were analyzed according to qualitative content analysis, as proposed by Mayring (Mayring, 2014), using the software MAXQDA12. The publications were screened for relevant text passages which, in a first step, were each assigned a descriptive code. These codes were then grouped if they described the same ethical aspect. These inductively derived codes were grouped in deductive categories and subcategories. They were regularly revised and altered to eliminate doubling or overlap to ensure the reliability of the coding system and the categories. Regular team meetings were held to discuss the coding procedure with all authors. The latter have academic backgrounds in medicine, applied ethics and philosophy.

RESULTS

The electronic database searches resulted in 307 publications published between 1988 and 2020. A total of 135 articles were identified by title abstract screening and the full texts were thoroughly examined based on the inclusion criteria. Eventually, 38 publications were included for systematic review. An additional 17 publications were identified by screening the citations. Fifty-four of these publications are written in English and one is written in German (see **Table 1** for the publications included; see **Figure 2** for the types of publication).

A total of 918 relevant text passages were identified in the 55 publications included. These text passages were given descriptive codes, which were then pooled to a total of 93 different ethical aspects. These codes were grouped into three main categories: *Process of testing*, *consequences of the test outcome* and *contextual challenges*. A total of 20 subcategories were introduced within these main categories to structure the results further (see **Table 2** for the coding system).

The following three main categories were established:

1) Process of testing: Ethical aspects concerning the procedure of genetic testing for rare diseases, the analysis of these tests and the delivery of the results to the patient and/or the family.
2) Consequences of the test outcome: Ethical aspects that result from the knowledge of the test result or the decisions made following the disclosure and patient reactions to the test result.
3) Contextual challenges: Ethical aspects that are associated with the circumstances and background of the tests, the diseases tested for and the test results.

Process of Testing

The category *process of testing* encompasses 36 ethical aspects in nine subcategories (see **Table 2** for the coding system and **Figure 3** for the categories and subcategories). These aspects most often relate to practical issues which are prominent in routine clinician-patient-interactions such as obtaining informed consent or interpreting the test results. Accessibility is a broadly discussed ethical issue starting with the necessary referral to a testing facility which, however, presupposes the suspicion of a rare genetic disorder and knowledge of the testing opportunities:

> "However, primary care physicians should be increasingly alerted to the new diagnostic options

TABLE 1 | Publications included.

1	Zhytnik L, Simm K, Salumets A, Peters M, Maasalu K. Reproductive options for families at risk of osteogenesis imperfect: A review. Orphanet J. Rare. Dis. 2020; 15(1): 128.
2	Umbach N, Beißbarth T, Bleckmann A, Duttge G, Ristau L, König A, et al. Clinical application of genomic high-throughput data: Infrastructural, ethical, legal and psychosocial aspects. Eur Neuropsychopharmacol. 2020; 31: 1–15.
3	Marshall DA, MacDonald KV, Heidenreich S, Hartley T, Bernier FP, Gillespie MK, et al. The value of diagnostic testing for parents of children with rare genetic diseases. Genet Med. 2019; 21(12): 2798–2806.
4	Houdayer F, Putois O, Bebonneau ML, Chaumet H, Joly L, Juif C, et al. Secondary findings from next generation sequencing: psychological and ethical issues. Family and patient perspectives. Eur J Med Genet. 2019; 62(10): 103711.
5	Bernard A, Herson A, Gargiulo M, Durr A. Reverse pre-symptomatic testing for Huntington disease: double disclosure when 25% at-risk children reveal the genetic status to their parent. Eur J Hum Genet. 2019; 27(1): 22–27.
6	Normand EA, Alaimo JT, Van den Veyver IB. Exome and genome sequencing in reproductive medicine. Fertil Steril. 2018; 109(2): 213–220.
7	Hayeems RZ, Boycott KM. Genome-wide sequencing technologies: a primer for paediatricians. Paediatr Child Health. 2018; 23(3): 191–197.
8	Boardman FK, Young PJ, Warren O, Griffiths FE. The role of experiential knowledge within attitudes towards genetic carrier screening: A comparison of people with and without experience of spinal muscular atrophy. Health Expect. 2018; 21(1): 201–211.
9	Tester DJ, Ackerman MJ. Evaluating the survivor or the relatives of those who do not survive: the role of genetic testing. Cardiol Young. 2017; 27: 19–24.
10	Ravenscroft G, Davis MR, Lamont P, Forrest A, Laing NG. New era in genetics of early-onset muscle disease: Breakthroughs and challenges. Sem Cell Dev Biol. 2017; 64: 160–170.
11	Hayward J, Bishop M, Rafi I, Davison V. Genomics in routine clinical care: what does this mean for primary care? Br J Gen Pract. 2017; 67(655): 58–59.
12	Allen S, Young E, Bowns B. Noninvasive prenatal diagnosis for single gene disorders. Curr Opin Obstet Gynecol. 2017; 29(2): 73–79.
13	Afroze B, Brown N. Ethical issues in managing Lysosomal storage disorders in children in low and middle income countries. Pak J Med Sci. 2017; 33(4): 1036–1041.
14	Verhoef TI, Hill M, Drury S, Mason S, Jenkins L, Morris S, et al. Non-invasive prenatal diagnosis (NIPD) for single gene disorders: cost analysis of NIPD and invasive testing pathways. Prenat Diagn. 2016; 36(7): 636–642.
15	Smith LD, Willig LK, Kingsmore SF. Whole-exome sequencing and whole-genome sequencing in critically ill neonates suspected to have single-gene disorders. Cold Spring Harb Perspect Med. 2016; 6(2): a023168.
16	Working Group for the Use of Genome-Wide Sequencing for Undiagnosed Rare Genetic Diseases in Ontario. 2016
17	Warman Chardon J, Beaulieu C, Hartley T, Boycott KM, Dyment DA. Axons to exons: the molecular diagnosis of rare neurological diseases by next-generation sequencing. Curr Neurol Neurosci Rep. 2015; 15(9): 64.
18	Skirton H, Goldsmith L, Chitty LS. An easy test but a hard decision: ethical issues concerning non-invasive prenatal testing for autosomal recessive disorders. Eur J Hum Genet. 2015; 23(8): 1004–1009.
19	Petrikin JE, Willig LK, Smith LD, Kingsmore SF. Rapid whole genome sequencing and precision neonatology. Semin Perinatol. 2015; 39(8): 623–631.
20	Nguyen MT, Charlebois K. The clinical utility of whole-exome sequencing in the context of rare diseases - the changing tides of medical practice. Clin Genet. 2015; 88(4): 313–319.
21	Klein H-G, Rost I. Current methods in genetic analysis: an approach for genetics-based preventive medicine. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz. 2015; 58(2): 113–120.
22	Sapp JC, Dong D, Stark C, Ivey LE, Hooker G, Biesecker LG, et al. Parental attitudes, values, and beliefs toward the return of results from exome sequencing in children. Clin Genet. 2014; 85(2): 120–126.
23	Might M, Wilsey M. The shifting model in clinical diagnostics: how next-generation sequencing and families are altering the way rare diseases are discovered, studied, and treated. Genet Med. 2014; 16(10): 736–737.
24	Lohmann K, Klein C. Next generation sequencing and the future of genetic diagnosis. Neurotherapeutics. 2014; 11(4): 699–707.
25	Lewis C, Hill M, Chitty LS. Non-invasive prenatal diagnosis for single gene disorders: experience of patients. Clin Genet. 2014; 85(4): 336–342.
26	Danielsson K, Mun LJ, Lordemann A, Mao J, Lin CH. Next-generation sequencing applied to rare diseases genomics. Expert Rev Mol Diagn. 2014; 14(4): 469–487.
27	Boardman FK. The expressivist objection to prenatal testing: the experiences of families living with genetic disease. Soc Sci Med. 2014; 107: 18–25.
28	Korf BR, Rehm HL. New approaches to molecular diagnosis. JAMA. 2013; 309(14): 1511–1521.
29	Kingsmore SF. Incidental swimming with millstones. Sci Transl Med. 2013; 5(194): 194ed10.
30	Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet. 2013; 14(10): 681–691.
31	Soden SE, Farrow EG, Saunders CJ, Lantos JD. Genomic medicine: evolving science, evolving ethics. Pers Med. 2012; 9(5): 523–528.
32	Makrythanasis P, Antonarakis SE. High-throughput sequencing and rare genetic diseases. Mol Syndromol. 2012; 3(5): 197–203.
33	Tester DJ, Ackerman MJ. Genetic testing for potentially lethal, highly treatable inherited cardiomyopathies/channelopathies in clinical practice. Circulation. 2011; 123(9): 1021–1037.
34	Kingsmore SF, Dinwiddie DL, Miller NA, Soden SE, Saunders CJ. Adopting orphans: comprehensive genetic testing of Mendelian diseases of childhood by next-generation sequencing. Expert Rev Mol Diagn. 2011; 11(8): 855–868.
35	Petrou M, Patrinos GP, Ansorge WJ. Genetic counseling and ethics in molecular diagnostics. In: Patrinos GP, Ansorge W (eds). Molecular Diagnostics. 2nd edn. (Academic Press, San Diego, 2010), pp. 537–548.
36	Fuentes J, Martin-Arribas MC. Bioethical issues in neuropsychiatric genetic disorders. Child Adolesc Psychiatr Clin N Am. 2007; 16(3): 649–661.
37	Lipinski SE, Lipinski MJ, Biesecker LG, Biesecker BB. Uncertainty and perceived personal control among parents of children with rare chromosome conditions: the role of genetic counseling. Am J Med Genet C Semin Med Genet. 2006; 142C(4): 232–240.
38	Dimichele D, Chuansumrit A, London AJ, Thompson AR, Cooper CG, Killian RM, et al. Ethical issues in haemophilia. Haemophilia. 2006; 12: 30–35.
39	Maddalena A, Bale S, Das S, Grody W, Richards S. Technical standards and guidelines: molecular genetic testing for ultra-rare disorders. Genet Med. 2005; 7(8): 571–583.
40	Kalfoglou AL, Scott J, Hudson K. PGD patients' and providers' attitudes to the use and regulation of preimplantation genetic diagnosis. Reprod BioMed Online. 2005; 11(4): 486–496.
41	Thomas SM. Society and ethics – the genetics of disease. Curr Opin Genet Dev. 2004; 14(3): 287–291.
42	Krajewski KM, Shy ME. Genetic testing in neuromuscular disease. Neurol Clin. 2004; 22(3): 481–508.

(Continued on following page)

TABLE 1 | *(Continued)* Publications included.

43	Delatycki BM, Powell LW, Allen KJ. Hereditary hemochromatosis genetic testing of at-risk children: What is the appropriate age? Genet Test. 2004; 8(2): 98–103.
44	Cox SM, Faucett WA, Chen B, Dequeker E, Boone DJ, McGovern MM, et al. International genetic testing. Genet Med. 2003; 5(3): 176–182.
45	Merz JF KA, Leonard DGB, Cho MK. Diagnostic testing falls the test. Nature. 2002: 577–579.
46	Gross ML. Ethics, policy, and rare genetic disorders: the case of Gaucher disease in Israel. Theor Med Bioeth. 2002; 23(2): 151–170.
47	Committee on Bioethics. Ethical issues with genetic testing in pediatrics. Pediatrics. 2001; 107: 1451–1455.
48	Ahmed S, Saleem M, Sultana N, Rashid Y, Waqar A, Anwar M et al. Prenatal diagnosis of beta-thalassaemia in Pakistan experience in a Muslim country. Prenat Diagn. 2000; 20: 378–383.
49	Pulst SM. Ethical issues in DNA testing. Muscle Nerve. 2000; 23(10): 1503–1507.
50	Thomas SM. Genomics: the implications for ethics and education. Br Med Bull. 1999; 55(2): 429–445.
51	Van der Riet AA, Van Hout BA, Rutten FF. Cost effectiveness of DNA diagnosis for four monogenic diseases. J Med Genet. 1998; 34: 741–745.
52	Gin BR. Genetic discrimination: Huntington's disease and the Americans with Disabilities Act. Columbia L Rev. 1997; 97(5): 1406–1434.
53	Biesecker LG. Orphan tests. Camb Q Healthc Ethics. 1996; 5(2): 300–306.
54	Terrenoire G. Huntington's Disease and the ethics of genetic prediction. J Med Ethics. 1992; 18: 79–85.
55	Morris M, Tyler A, Harper PS. Adoption and genetic prediction for Huntington's disease. Lancet. 1988; 2(8619): 1069–1070.

for patients with rare, unclassified conditions who may benefit from NGS-based genetic testing, and refer such patients to a center of rare diseases or similar tertiary care facility."(Lohmann and Klein, 2014)

A challenge is seen in finding local or even national laboratories providing adequate testing for rare diseases and especially ultra-rare diseases:

> "In contrast, for rare genetic conditions, testing may be available from very few laboratories, necessitating specimen and patient referrals across national boundaries." (Cox et al., 2003)

Additionally, tests might be offered in research settings only, which further complicates the process of counselling:

> "[. . .] some tests exist in a gray area between the research and clinical worlds, either temporarily because they are in transition, or permanently because there is no market for the test." (Biesecker, 1996)

An inevitable component of genetic counselling is obtaining informed consent for the testing procedure and the disclosure of the results. In view of the rapidly evolving field of genetic technologies and the very specific characters of the genetic disorders the counsellor is confronted with major communicative challenges:

> "[. . .] individualization may need to be integrated more into the informed consent process in order to accommodate individual preferences, allowing individuals the autonomy to opt in or out of receiving more extensive information regarding results." (Danielsson et al., 2014)

The subcategory "timing of testing" is very prominent in the ethical literature included in the review. Several different time frames are discussed, including preimplantation of genetic testing, genetic testing during pregnancy, genetic testing in minors or testing for late onset diseases. These are especially sensitive topics about which patients might have preconceived notions which need to be respectfully addressed during counselling. Only post mortem genetic testing has not been prominently discussed even though coming with difficulties in obtaining consent and respect for the deceased.

Consequences of the Test Outcome

The category *consequences of the test outcome* consists of 37 ethical aspects in seven subcategories. It deals with aspects resulting directly from the disclosure of the outcome (see **Table 2** for the coding system and **Figure 3** for the categories and subcategories). This category is relevant for a wide range of health care professionals as it focuses on potentially far-reaching clinical consequences and has major implications for provider-patient-communication.

Some of the consequences of the test outcome were judged as *benefits*; others are rather negatively connoted. The positive aspects include the knowledge about the condition and its therapy. The diagnosis ideally leads to accessing treatment options but is sometimes viewed as insufficient if no direct treatment is available. This situation is challenging and should be anticipated in research and clinical practice:

> "Even if we know the genes involved and the loci associated with the condition, this does not mean that we have an immediate specific line of treatment. This mismatch between risk information and the possibility of effective treatment is one of the sources of ethical, legal, and social conflicts with which researchers and clinicians should be familiar." (Fuentes and Martín-Arribas, 2007)

But also less obvious options such as becoming part of a patient self-help group and connecting *via* social media with individuals and families with similar diagnoses might be the consequence of a molecular diagnosis:

> "A diagnosis also provides the family an opportunity to connect with disease-specific support groups so that

TABLE 2 | Coding system.

Main category	Sub-category	Ethical aspect	Number of occurences	References
Process of testing			402	
	Availability		73	
		Collaboration of laboratories/specialists	10	(23) (24) (32) (34) (44) (53)
		Access to genetic testing	10	(1) (16) (20) (24) (28) (32) (39) (53)
		Research laboratories	43	(3) (20) (24) (30) (32) (33) (36) (39) (41) (42) (44) (49) (50) (53)
		Clinical laboratories	9	(16) (32) (33) (39) (44)
		Direct to consumer testing	1	(31)
	Consent		52	
		Informed consent process	39	(2) (9) (12) (15) (16) (18) (19) (20) (22) (26) (31) (33) (36) (38) (39) (41) (47) (50) (54)
		Consent with minors	3	(47) (49) (55)
		The right to know	4	(13) (19) (26) (54)
		The right not to know	5	(2) (8) (9) (21) (54)
		Tiered or dynamic forms of consent	1	(2)
	Genetic counseling		48	
		Difficulties of counseling	12	(1) (21) (32) (34) (37) (50) (54)
		Requirements	30	(1) (16) (19) (21) (28) (31) (33) (36) (37) (44)
		Retrospective counseling	3	(48) (51)
		Importance of genetic counseling	3	(9) (50)
	Timing of testing		73	
		Testing minors	7	(4) (25) (31) (47) (49)
		Relevance of timing	5	(6) (7) (13) (49) (55)
		Preimplantation genetic testing	34	(25) (27) (40) (47) (54)
		Testing for late-onset diseases	21	(19) (26) (31) (40) (41) (43) (47) (54) (55)
		Postmortem genetic testing	6	(9) (16) (17) (25) (27) (40) (47) (54)
	Interpretation of results		28	
		Interpretation	13	(9) (12) (19) (20) (26) (31) (32) (33) (50)
		Consequences of inaccurate interpretation	15	(17) (19) (26) (29) (33) (41) (47)
	Regulations and standards		56	
		Laboratory practice issues	17	(24) (44) (49) (53)
		Patient management issues	7	(44)
		Need for standards	13	(24) (28) (40) (44) (53)
		Patient/family as decision-maker	6	(40) (46) (54) (55)
		Protection from unethical practices	4	(20) (40) (53)
		Regulations creating barriers	9	(40)
	Physicians		22	
		Increased demands on physicians	17	(1) (7) (20) (24) (28) (29) (30) (31) (36) (37) (49)
		Family-professional collaboration	5	(23) (24)
	Reasons for testing		30	
		Clinical suspicion	7	(8) (22) (33)
		Desire to offer proper care	10	(1) (8) (14) (22) (31) (54)
		The need to know	9	(5) (22) (33)
		Reproductive choice	4	(1) (22) (47) (54)
	Other		20	
		Disclosure and access to the results	14	(2) (9) (26) (31) (33) (46) (54)
		Reasons not to test	6	(5)
Consequences of the test outcome			384	
	Diagnosis		78	
		End of diagnostic odyssey	15	(3) (6) (7) (10) (11) (17) (20) (23) (24) (29) (30) (34)
		Diagnostic certainty	31	(3) (7) (8) (9) (10) (11) (14) (15) (19) (20) (24) (25) (28) (31) (34) (38) (47) (49) (50)
		Prognosis	7	(7) (10) (15) (24) (31) (41) (51)
		Opportunities as a result of receiving diagnosis	12	(3) (7) (10) (14) (15) (25) (34) (37)
		Not receiving a molecular diagnosis	11	(17) (30) (33) (34)
		Positive effects of DNA diagnosis	1	(51)
		Social, personal and medical impacts of diagnosis	1	(3)
	Actionability of results		81	
		Access to disease-specific services	11	(15) (23) (24) (34) (54)
		Variants of unknown significance	5	(3) (9) (17) (19)
		Testing in the absence of therapeutic benefits	10	(6) (30) (32) (36) (49) (54)
		Prevention/alleviation of disease and suffering	25	(1) (2) (8) (10) (13) (15) (19) (25) (29) (34) (40) (47) (48) (50) (51)
		Disease management, therapy and interventions	30	(2) (3) (6) (10) (19) (24) (26) (29) (33) (34) (38) (41) (52)

(Continued on following page)

TABLE 2 | *(Continued)* Coding system.

Main category	Sub-category	Ethical aspect	Number of occurences	References
	Incidental findings		53	
		Handling of incidental findings	14	(3) (2) (4) (7) (17) (19) (22) (24) (26) (31) (32) (36) (42) (49)
		Consequences of incidental findings	8	(4) (17) (26) (31) (42) (49)
		Consenting to receive incidental findings	8	(4) (17) (19) (26) (32) (49)
		Incidental findings in children	6	(7) (22) (26)
		Reporting recommendations	13	(7) (16) (17) (19) (26) (31) (32)
		Measures to decrease incidental findings	3	(10) (17) (31)
		Controversy: Proactively searching for unsolicited information	1	(7)
	Stigma and discrimination		41	
		Impact of stigma and discrimination	8	(1) (2) (8) (9) (28) (33) (38)
		Legislation to address discrimination	3	(28) (41)
		Discrimination by insurance companies	7	(21) (40) (41) (49) (50)
		Discrimination at the workplace	8	(21) (41) (50) (52)
		Adoption agencies/child welfare institutions	3	(52) (55)
		Other types of stigma and discrimination	11	(3) (31) (35) (40) (47) (52)
		Genetic testing used against people	1	(31)
	Family planning		59	
		Informed decision-making	17	(1) (2) (3) (6) (8) (10) (24) (27) (34) (42) (50) (52)
		Abortion/Termination	35	(1) (6) (10) (12) (13) (14) (18) (25) (27) (31) (35) (41) (46) (50) (51)
		Implications for future pregnancies	6	(1) (6) (8) (31)
		Social consequences of private reproductive decisions	1	(40)
	Involvement of relatives		41	
		Information about people not directly tested	4	(2) (9) (36) (49)
		Relevance of results to family members/others	17	(4) (5) (9) (11) (26) (28) (33) (36) (42) (46) (49) (50) (54)
		Disclosure to family	14	(2) (5) (9) (26) (28) (33) (41) (46) (49) (54)
		Paternal rights	6	(12) (18)
	Other		31	
		Uncertainty due to implications of the test result	8	(1) (36) (37) (46) (54)
		Awareness of disease	4	(8) (21) (34)
		Distress and adverse effects	19	(1) (3) (4) (5) (9) (22) (33) (34) (36) (47) (55)
Contextual challenges			132	
	Increased pressure to test		9	
		Coerced testing	4	(12) (25) (33) (49)
		Routinization of test usage	3	(12) (18) (27)
		Testing is optional	1	(6)
		Pressure to test in order to eradicate disease	1	(54)
	Economic aspects		40	
		Commercial interests restricting testing	9	(1) (14) (34) (40) (53)
		Dilemma if expensive test is used for information only	2	(14)
		Cost saving by genetic testing	16	(3) (6) (10) (13) (15) (19) (34) (40) (51)
		Genetic testing is expensive	7	(12) (14) (33) (40) (46) (53)
		Patents	3	(45)
		Large number of disorders is a cost challenge	1	(14)
		Difficulties to obtain funding	2	(15) (20)
	Data		24	
		Infrastructural challenges	7	(2) (26) (41) (49)
		Privacy concerns	11	(26) (33) (41) (46) (50) (54)
		Third parties using the data	2	(41) (49)
		Data sharing	4	(23) (26)
	Other		59	
		Rarity as a challenge	7	(12) (32) (34) (53)
		Difficulties in test developement	8	(20) (31) (53)
		Cultural differences	7	(1) (18) (48)
		Public understanding of genetic testing and rare diseases	10	(1) (27) (31) (40) (46)
		Effects on people living with a disability	6	(1) (18) (27) (40)
		Other ethical dilemmas	21	(1) (7) (8) (12) (15) (19) (20) (26) (31) (40) (41) (46) (53)

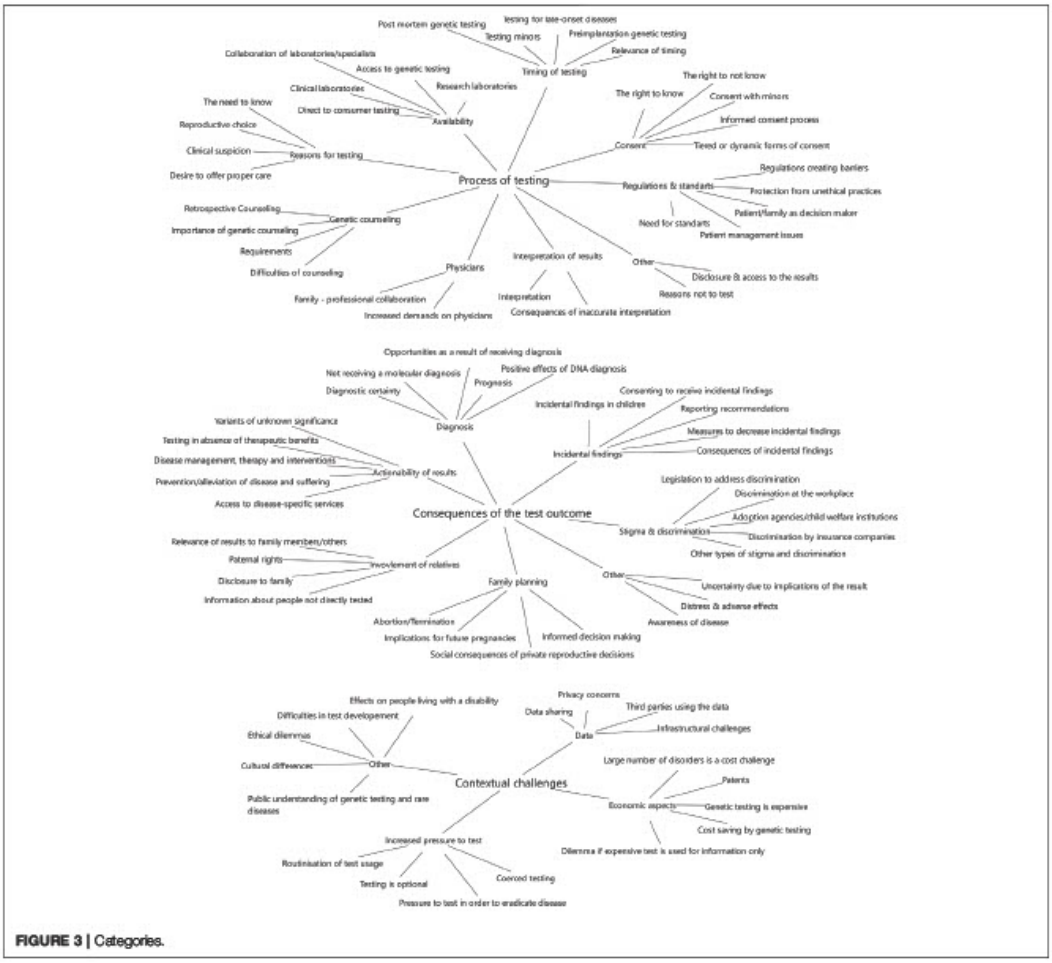

FIGURE 3 | Categories.

> they might meet others affected by the same rare disorder and exchange information about useful therapies and educational strategies." (Kingsmore et al., 2011)

This community aspect is particularly relevant in situations where no conventional treatment options are available. In this case interprofessional care plays a prominent role as an increased coordination of care among providers will become necessary to provide best supportive care.

Further ethical issues involve the relevance of the test result for people who are not directly tested. By disclosure of their results the family members learn of very private information about themselves (and further relatives) which they did not consent to but if not disclosed might have an interest to know. This ambiguous situation needs to be extensively addressed and prepared for during counselling:

> "Ethical challenges are generated when information produced by the results may affect third parties, including family members not directly involved in the process." (Fuentes and Martín-Arribas, 2007)

Contextual Challenges

The category *contextual challenges* includes 21 ethical aspects in four subcategories (see **Table 2** for the coding system and **Figure 3** for the categories and subcategories). These aspects do not refer directly to the procedure or result of the test but

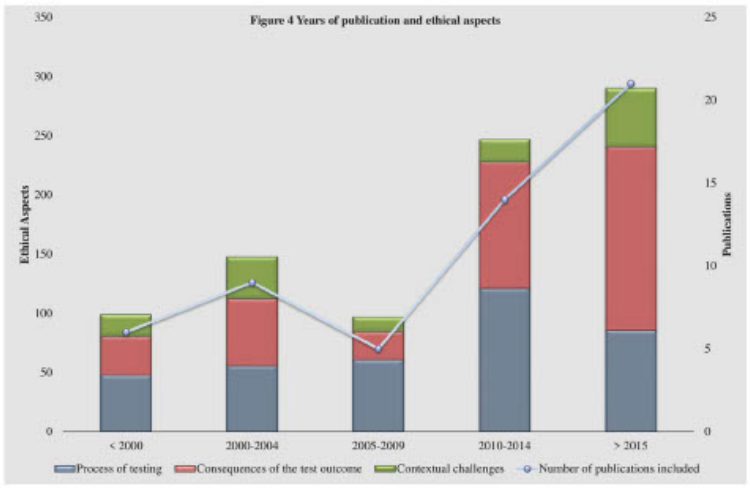

FIGURE 4 | Years of publication and ethical aspects.

rather address the general circumstances of genetic testing for rare diseases, including societal aspects. In this, the contextual aspects typically lie out of the direct sphere of influence of clinicians and genetic counsellors but touch more generally on health care structures, policies and frameworks.

For example, it is argued, that it is inevitable to be aware of contextual challenges in order to integrate patients' experiences and expectations into appropriate support and care. Optimal research and care, however, are often hindered by the contingent character of rare diseases:

> "The application of evidence-based medicine in the field of genetic testing often remains questionable, because rare diseases imply a difficulty to meet the criteria required in terms of sample size for clinical trials or sound genetic research." (Fuentes and Martín-Arribas, 2007)

Further ethical issues extend to economic aspects influencing the provision and development of genetic tests for rare diseases. Depending of the point of view genetic testing for rare diseases can be very cost effective as in cutting back the diagnostic odyssey of many years but are, as a single test, often still expensive. Here societal dialogue is necessary to examine the costs and benefits not only for the individual patient but also the society as a whole. On a macro level the financing of healthcare systems prominently intersects with the provision of care:

> "Patients with rare diseases traditionally experience a prolonged and expensive diagnostic odyssey culminating in a delayed diagnosis or, frequently, no diagnosis at all. [...] this diagnostic odyssey is a financial burden to the health-care system, costing more than US $10,000 per patient." (Marshall et al., 2019)

An aspect commonly brought up in the economic discussion is the question of testing without consequences, when the test is used for information purposes only. This leads to delicate situations in clinical care, for example, when such a testing is performed during pregnancy:

> "The expected increased uptake of NIPD [non-invasive prenatal diagnosis] [...] highlight the ethical issues associated with using NIPD for information only and the appropriateness of directing resources to a test that would not change pregnancy management [...]. Decisions about how NIPD is offered will need to take this concern into consideration, keeping in mind [...] the clinical and psychological benefits afforded by NIPD which include early the possibility of reassurance or provision of information for planning and preparation of the birth of an affected child, as well as the potential of access to surgical termination of pregnancy." (Verhoef et al., 2016)

The contextual challenges of genetic testing for rare diseases eventually include different ethical fields such as the methodology of clinical trials, issues of distributional justice and dealing with diagnoses without appropriate treatment options.

Some shifts in the perspectives of the discussion of ethical aspects over the past 30 years are visible within the coding system

(See Figure 4 Years of publication and ethical aspects). Literature published in the 1990s and early 2000s focuses more on practical aspects, such as regulation and standards concerning laboratory practices (Terrenoire, 1992; Biesecker, 1996; Pulst, 2000; Cox et al., 2003). At that time, the establishment of guidelines was essential to address appropriately the rapidly developing technologies. Additionally, uncertainties about the possible impacts of the fast rising usage of genetic testing technologies were widely prevalent. Possible scenarios of discrimination resulting from the disclosure of a genetic test result were brought up (Thomas, 1999; Gin, 1997; Committee on Bioethics, 2001; Thomas, 2004) and the handling and security of genetic data was reflected (Terrenoire, 1992; Thomas, 1999; Pulst, 2000; Gross, 2002; Thomas, 2004). Interestingly, data management and security remained important issues to this day but have left the center of the debate (Cox et al., 2003; Umbach et al., 2020). The perspectives of more recent publications, in alignment with advancements in genetic testing such as whole genome sequencing, have shifted to more specific questions, such as the handling of incidental findings (Marshall et al., 2019; Houdayer et al., 2019; Umbach et al., 2020). The obtainment of incidental findings is closely related to the establishment of new technologies (Umbach et al., 2020). This raises questions regarding their utility, consent and, thereby, aggravates the appropriate delivery of results (Umbach et al., 2020). Similarly, the indispensable role of the physician in interpreting and disclosing the results (Nguyen and Charlebois, 2015; Hayeems and Boycott, 2018; Zhytnik et al., 2020) and their relationship to the patient (Lohmann and Klein, 2014; Might and Wilsey, 2014) have gained significance in the literature.

DISCUSSION

The appropriate handling of ethical issues is a requisite for adequate care in patients undergoing genetic testing for rare diseases. A variety of publications, using different methods and focal points, dealing with a multiplicity of ethical aspects were identified in this review. Positive, negative and ambiguous aspects were found which portray the challenges with which individuals, families, professionals, healthcare systems and society are faced. A thorough understanding of their diversity and complexity is a prerequisite for attending to ethical aspects systematically and transparently. In the light of the diversity of ethical issues one aspect from each major coding category will be discussed exemplarily in the following while also highlighting the intersection with other relevant ethical aspects.

Process of Testing

An aspect which was discussed most controversially in the literature published in the recent 10 years and which is of particular relevance to rare diseases, in contrast to more common diseases, is the availability and accessibility of genetic testing. Genetic testing specifically in the research setting was intensively discussed by various authors (Biesecker, 1996; Fuentes and Martín-Arribas, 2007; Marshall et al., 2019). Many patients with a suspected rare disease find themselves in a situation where their only access to a genetic test is to be found in a study context, since many genetic tests for rare diseases are unattractive to clinical laboratories for their low profitability (Biesecker, 1996; Thomas, 2004; Marshall et al., 2019).

Missing opportunities to undergo a genetic test outside the research setting might compromise the key ethical requirement of voluntary participation in research. In addition, other regulations apply to research laboratories than to clinical laboratories (Biesecker, 1996; Pulst, 2000; Might and Wilsey, 2014). Standards for test validity and reliability differ from those in clinical laboratories, further complicating patient communication and the utilization of results (Biesecker, 1996; Danielsson et al., 2014). Also standards for the return of results vary, patients often receive the results only after completion of the study, while appropriate counseling is not always guaranteed (Krajewski and Shy, 2004; Danielsson et al., 2014; Might and Wilsey, 2014). This leaves the referring physician with a particularly difficult task of navigating this very specific setting with their patient and the family.

The intersection between clinical care and study context is only superficially addressed in national and international policies. One example is "The Council of Europe Convention on Human Rights and Biomedicine" which also covers genetic testing. Article 12 of the Convention limits the usage of predictive genetic testing to that it "[. . .] may be performed only for health purposes or for scientific research linked to health purposes [. . .]" (European Union, 1997). Thereby, genetic testing in research setting is technically covered by the convention as a minimum standard but no elaboration is offered concerning this specific situation. Furthermore, as of June 2020 this convention has only been ratified by 29 members of the European Council (Tester and Ackermann, 2017).

Consequences of the Test Outcome

One frequently discussed outcome of genetic testing is the possibility of facing stigma and discrimination (Korf and Rehm, 2013; Dimichele et al., 2006; Tester and Ackermann, 2017). According to the definition of E. Goffman a stigma describes a distinctive feature of a person which is linked to a negative stereotype and is considered "deeply discrediting" by societal standards (Goffman, 1963). Stigma and discrimination might come in a multitude of forms such as regulatory issues regarding insurance or employment or social issues such as exclusion from social activities.(Williams et al., 2010; Tester and Ackerman, 2011). Stigmatization can apply not only to people affected by a diagnosis, but also those with a positive carrier status. In specific cultural contexts this stigmatization could cause gender specific discrimination and reproductive restrictions for some women (Zhytnik et al., 2020). In the United States, as an example, in 2009 the Genetic Information Nondiscrimination Act (GINA) was signed which protects patients from being denied employment and health insurance based on their genetic test results (Tester and

Ackerman, 2011). This menace of stigmatization and discrimination raises the questions, who should have access to genetic information and how to best ensure confidentiality and data protection while still utilizing the test results to their full potential (Umbach et al., 2020).

One aspect which was not represented in this review is that stigma and genetic discrimination are not universal experiences for everyone diagnosed with a genetic disease but highly individual experiences which might even have differing outcomes (Williams et al., 2010). A genetic cause is not automatically connected to a sense of being stigmatized (Sankar et al., 2006). A hereditary disease might also mean growing up among people with the same condition and impairments. Therefore, a genetic diagnosis might become a positive feature of identity, as for example being the basis for family cohesiveness, or as a link to one's ancestry (Sankar et al., 2006).

Additionally, a diagnosis might also imply a connection to other affected individuals outside the family which can be accessed locally in the form of support groups or globally in online supportive networks (Kingsmore et al., 2011; Petrikin et al., 2015). Useful information about the condition, potential treatment options or supportive services can be exchanged alleviating the commonly sparse information available about genetic conditions. Even other forms of support such as psychological or spiritual assistance will be easier to access once the condition and prognosis are clear (Petrikin et al., 2015). This can be especially beneficial in situations where a diagnosis does not come along with curative therapeutic options.

Contextual Challenges

Unexpectedly, not one of the publications included has economics aspects as its main focus. Of the publications included, 17 discuss an economic aspect but only four publications include two or more aspects. The reason for this neglect of economic aspects remains rather unclear. The EU and several individual states have legislations in place to foster the research on medicinal products for rare diseases as well as the provision of those (European Union, 2008). These legislations do not include medical devices such as genetic tests (European Union, 2008). Therefore, laboratories are not provided with an economic incentive for developing such tests (Hayeems and Boycott, 2018). Some of the authors voiced concern about the exclusivity of patents on genes and how they contribute significantly to the high prices of genetic tests for rare diseases (Nguyen and Charlebois, 2015). Thereby, the tests become even less attractive to clinical laboratories, perpetuating the testing in research laboratories discussed later (Nguyen and Charlebois, 2015). Patented genes offer the owner a monopoly not only of the initial diagnostic test but every diagnostic method using the same DNA sequence (Might and Wilsey, 2014). Thereby, the already difficult access to testing is at risk of being further compromised on behalf of patent interests.

Limitations

This review aims to offer an empirical analysis portraying the diversity and complexity of ethical aspects relevant to genetic testing for rare diseases. The purpose of this review was not to quantify how often certain ethical aspects have been mentioned in the literature. Furthermore, it is important to understand that the frequency with which an ethical aspect occurs does not necessarily correlate to its relevance or importance. The ethical aspects displayed in this review are limited to the publications found via the three databases accessed (Pubmed, Science Direct, Web of Science). Prior to the final search, an exploratory search of several databases was conducted and the three databases subsequently accessed were identified as delivering the highest number of relevant results. Additionally, the neglect of literature written in languages other than English or German limits this review.

No quality appraisal for the included literature was performed due to the lack of quality assessment tools for systematic reviews of ethical literature (Mertz, 2019). Therefore, all publications fitting the inclusion criteria were included and it is up to the readership to critically judge the quality of the ethical aspects presented.

CONCLUSION

A lack of knowledge and comprehension of the fast-paced developments of genetic testing among professionals poses an obstacle to accessing comprehensive testing (Nguyen and Charlebois, 2015). Many physicians find themselves insufficiently equipped for processing the amount of information that accompanies a genetic testing result for a rare disease and feel overwhelmed when navigating the complex ethical aspects associated (Pulst, 2000; Sankar et al., 2006; Soden et al., 2012). This is only intensified by the diversity of rare diseases themselves and the widespread lack of knowledge and awareness about them, and needs to be addressed (Soden et al., 2012).

This review found that not many physicians find themselves in a position where they feel knowledgeable enough to order and conduct genetic testing, especially for rare diseases (Soden et al., 2012). An effective cooperation with genetic counsellors forms the basis to solving this issue. These counsellors are specially trained non-physician experts in genetics who should be an integral part of every inter-professional genetics team (Soden et al., 2012; Boycott et al., 2013; Fuentes and Martín-Arribas, 2007).

However, this should, on the other hand, not deviate from the much needed extension of the education of physicians and other healthcare professionals to deliberately cover the advantages and disadvantages of genetic testing in the context of rare diseases, including not only medical subjects but also the ethical and legal issues presented in this review (Gin, 1997; Soden et al., 2012; Umbach et al., 2020).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JK, SS, and RM developed the research question; JK and RM did the data collection; SS, JK, RM, AA, and ML contributed analytic tools and data analysis; JK drafted the article. All authors revised the article. All authors read and approved the final article.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

e. Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät und keiner anderen wissenschaftlichen Einrichtung vorgelegt worden.

Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

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