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"Ethical, Legal and Social/Societal Implications (ELSI) of Recall-by-Genotype (RbG) approaches in the Cooperative Health Research in South Tyrol (CHRIS) study on genetic risk factors of Parkinson's disease (PD)"

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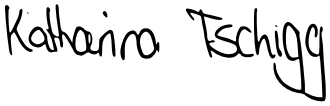
Declaration of authorship

This chapter serves as a formal declaration of authorship, outlining the authors' contributions to the research presented in this thesis.

'*I, Katharina Tschigg, confirm that this is my own work and the use of all material from other sources has been properly and fully acknowledged'*.



Preface

This thesis was developed during the three-year doctoral program of the International PhD Program in Biomolecular Sciences, Department of Cellular, Computational, and Integrative Biology (CIBIO) of the University of Trento in Collaboration with the Institute for Biomedicine, Eurac Research, Bolzano, Italy & Affiliated Institute of the University of Lübeck, Germany.

Most of the work has been conducted at the Institute for Biomedicine and the associated study centre in Schlanders.

I spent three months (1/04/2022–30/06/2022) at the Institute for Science in Society, Radboud University, Netherlands, collaborating with Luca Consoli to design and hold teaching sessions.

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Bolzano, June 2023

Katharina Tschigg

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‘*I was not always the best student with the highest grades,*
but my teachers saw something in me and tried to encourage me’.
MAY-BRITT MOSER - ("The Nobel Prize | Women who changed science | May-Britt Moser," 2019)

I want to express my appreciation to Deborah Mascalzoni, whose unwavering guidance and support allowed me to embark on this fascinating path towards my PhD. Her mentorship and collaboration with Roberta Biasiotto and Ciara Staunton have allowed me to work on an interdisciplinary project and engage in stimulating scientific discussions that have contributed to my growth as an individual and an independent scientist. In addition, I am deeply grateful for the support and guidance provided by the CHRIS team and the researchers at the Institute for Biomedicine.

In a special note of gratitude, I extend my heartfelt appreciation to Luca Consoli. His dedicated mentorship, unwavering support, and friendship have been a cornerstone throughout the entirety of these three years. Luca's openness to sharing his expertise and his boundless encouragement and inspiration have been instrumental in shaping my research path and instilling in me the confidence to tackle challenges.

My deepest gratitude goes to my family. In particular, I would like to thank my sister and my partner for their tireless encouragement and hours of scholarly discussions during my PhD journey.

Contents

List of Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
CHRIS	Cooperative Health Research in South Tyrol
EHR	Electronic Health Record
ELSI	Ethical, Legal, and Social/Societal Implications
ELSA	Ethical, Legal, and Social/Societal Aspects
FGD	Focus Group Discussions
GDPR	General Data Protection Regulation
GDR	Genotype Driven Research/Recall/Recruitment
GBR	Genotype-Based Recall
GDRR	Genotype Driven Research Recruitment
GWAS	Genome-Wide Association Studies
MR	Mendelian randomisation
NGS	Next-Generation Sequencing
PD	Parkinson's Disease
PDGR	Participant-Driven Genomic Research
PRKN	Parkin
RbG	Recall by Genotype
RbGsv	Recall by Genotype single variants
RbGmv	Recall by Genotype multiple variants
RoRR	Return of Research Results
ROR	Return of individual genomic Results
RRI	Responsible Research and Innovation
STS	Science and Technology Studies
WGS	Whole- Genome-Sequencing

Disclaimer

We will use RbG as an umbrella term for the following: recall-by-genotype, genotype-driven-recall, genotype-driven-recruitment, genotype-driven-recontact, genotype-driven-research-recruitment, genotype-guided-recall, genotype-guided-recruitment, genotype-guided-research- recruitment, genotype-informed-recall, genotype-informed-recruitment, genotype- informed-recontact, genotype-based-recall, genotype-based-recontact, genotype-based-recruitment, genotype-informed-recruitment, genotype- informed-recall, genotype-informed-recontact, genotype-informed-recall, recruit-by- genotype, recontact-by- genotype.

Some of the results included in this cumulative thesis are also contained in the published manuscripts and were adapted and aligned to match the style of this thesis in terms of citations, table numbers, and other relevant factors.

Abstract

Recall-by-genotype (RbG) strategies are bottom-up approaches to conducting targeted follow-up studies or substudies with eligible participants. They use specific genetic information derived from previous genome-wide association studies or whole-genome sequencing enabled by next-generation sequencing.

Genetic information may be partially disclosed when certain participants are recalled for RbG studies, and information on the study design and eligibility criteria is provided. These distinguishing peculiarities of RbG approaches have ethical, legal, and social/societal implications (ELSI).

In this thesis, we present and discuss the results of research on the ELSI aspects of RbG approaches and within the Cooperative Health Research in South Tyrol (CHRIS) studies (RbG1, RbG2) on genetic risk factors of Parkinson's disease (PD).

We used various qualitative and quantitative methods, including interviews, surveys and focus group discussions (FGD). Thereby, we sought to address the need for qualitative data from diverse stakeholders, including critical voices in the CHRIS research ecosystem, such as participants, researchers, ethics board members, and study assistants, to develop effective recall and communication strategies through a collaborative approach refining the CHRIS RbG policy.

The exploration began with a literature review revealing the explicit and implicit ELSI of RbG study designs. It uncovered a consensus

on the significant ethical challenges RbG poses while highlighting the diversity in consent models and Return of Research Results (RoRR) policies employed in different research and biobanking contexts.

Then, a secondary analysis of interviews and surveys from a mixed-methods study with CHRIS RbG participants from the RbG pilot study (RbG1) followed. Alongside the second follow-up RbG study (RbG2) study, we then designed a survey, informed by the results of RbG1, to gather further perspectives on their experience of an RbG study, and other fundamental considerations pertinent to engagement and communication in RbG studies. Then, to explore the operational and practical aspects of RbG studies, we identified the relevant stakeholders who shape and decide on RbG study designs. Consequently, we designed and conducted FGD to examine stakeholder perspectives on the RbG study design, communication, and disclosure strategies. Further, we collected feedback and views from CHRIS study personnel and coordinators who accompanied the RbG1 and 2 study process. Finally, we conducted a large-scale survey with CHRIS participants to strengthen the conclusions of previous empirical research. This collaborative approach aims to refine the CHRIS RbG policy, develop effective recruitment and communication strategies, and promote transparency.

The study's findings underscore the value of personalised engagement and sensitive communication through tailored disclosure and communication strategies. Stakeholder views on ELSI in RbG studies reveal diversity, highlighting the need for

adaptable approaches aligned with study contexts. Overall, the results suggest that participants are highly interested in receiving information on carrier status on the genetic variations investigated by the RbG study, but views and motivations were heterogeneous. This adds to the complexity of integrating these insights into communication strategies and disclosure policies. More research is necessary to investigate the effects of various disclosure strategies, the impact of disclosure on awareness, and how framing affects participants' reception of study-specific information.

Thesis Outline

This section outlines the structure of my doctoral research, emphasising its interconnected chapters. Each chapter contributes to the overall aim of investigating the ELSI of RbG and evaluating the CHRIS RbG disclosure policies and communication strategies.

The **Introduction** provides a comprehensive context for the subsequent chapters and sections, focusing on the following:

Ethical, legal and social/societal implications (ELSI)

Recall-by-genotype (RbG)

The Cooperative Health Research in South Tyrol (CHRIS) study and biobank

Three chapters report the research results and the author's contribution is appended at the end of each chapter.

Chapter 1 extends to identifying and contextualising ELSI intrinsic to RbG study designs through a published scoping review. This chapter has already been published in the following publication, with minor changes to harmonise the thesis:

> **Tschigg, K**., Consoli, L., Biasiotto, R., & Mascalzoni, D. (2022). Ethical, legal and social/societal implications (ELSI) of recall-by-genotype (RbG) and genotype-driven-research (GDR) approaches: a scoping review. Eur. J. Hum. Genet., 30, 1000–1010. Doi: 10.1038/s41431-022-01120-y

Chapter 2 explores the perspectives of CHRIS participants in the RbG study, published as follows:

> Biasiotto, R., Kösters, M., **Tschigg, K**., Pramstaller, P. P., Brüggemann, N., Borsche, M., …Mascalzoni, D. (2023). Participant perspective on the recall-by-genotype research

approach: a mixed-method embedded study with participants of the CHRIS study. Eur. J. Hum. Genet., 1–10. Doi: 10.1038/s41431-022-01277-6

Chapter 3 comprehensively examines CHRIS participants' perspectives regarding disclosure and communication strategies for RbG studies. The manuscript is finalised, awaiting the consent of the Access Committee of the Institute of Biomedicine, all authors have agreed to submit the manuscript to the Journal of BMC Medical Ethics.

The **Discussion and Conclusion** section synthesises participants' perspectives and other findings from the research process to discuss them and inform policies and communication strategies for RbG studies.

The **Appendix** serves as a repository of supplementary materials utilised throughout the multistage study design.

Ethical, Legal, and Social/Societal Implications

This chapter explores ethical, legal, and social/societal implications (ELSI) and provides a comprehensive exploration of the multifaceted dimensions of ELSI research, shedding light on its historical evolution, methodologies employed, stakeholder engagement practices, and the intricate challenges researchers face. Moving forward, this chapter delves into the pivotal role of informed consent in biobanks, dissecting its evolution, requirements, and changing ethical guidelines. It further illustrates the shifting perspectives and debates surrounding consent comprehension, ultimately aiming to illuminate the nuanced interplay among ethics, law, and societal considerations in the realm of genetic research.

A Brief History of ELSI in Genetic Research

In 1988, James Watson, the Director of the Human Genome Project, announced that the various implications of genomics should receive both effort and funding. In 1990, U.S. Congress authorised funding for the ELSI Research Program as part of the Human Genome Project to investigate the ethical, legal, and social implications of the research field (Parker et al., 2019). The ELSI Research Program emerged as a response to concerns regarding potential unintended social consequences such as unwanted disclosures or the misuse of sensitive information. Accordingly, 3–5% of the budget was

allocated to funding projects that examined ELSI issues in genetics and genomics research (Conley et al., 2020).

From 1994 to 1998, the 4th European Union Framework Program introduced 'ELSA' as a funding label for research related to the ethical, legal, and social aspects of novel sciences and technologies to encourage various activities, such as stakeholder dialogue and education (Dolan et al., 2022; Stegmaier, 2009; Zwart et al., 2014). ELSA funding is used to fund activities that allow proximity to obtain a participant–observer perspective and provide a public and academic forum to address urgent societal issues that emerge in this context (Stegmaier, 2009; Zwart et al., 2014).

From 2002 to 2012, the Economic and Social Research Council in the United Kingdom funded various centers and institutions to examine the economic and social implications of genomic science and technologies; as a result, the Economic and Social Research Council and the Genomics Network were formed (Dolan et al., 2022; Hilgartner et al., 2017; Kosseim & Chapman, 2011).

Later, in light of a new label in the context of EU funding, such as Horizon 2020, Responsible Research and Innovation (RRI) emerged as an approach. RRI aims to integrate societal research and interaction into science and technology practices while maintaining some of the core principles of ELSA, such as proximity, focus on co-creation, and stakeholder participation throughout the process (Zwart et al., 2014). Various philosophers, such as Michel Serres (1972), had argued for proximity to science in an era of disruptive change long before ELSA existed (Zwart et al., 2014).

From 2013 to 2020, the European Commission incorporated RRI as a vital aspect of the Horizon 2020 Framework Program for Research and Innovation (Dolan et al., 2022). A subprogram titled Science with and for Society was assigned responsibility for RRI, focusing on themes such as public engagement, open access, gender, ethics, and science education (Dolan et al., 2022; Hartman et al., 2020; Rip, 2016).

Overall, the historical trajectory of ELSI in genetic research reflects an ongoing commitment to address the broader implications of scientific advancements and to ensure that research and innovation align with societal values, needs, and aspirations. As the field continues to evolve, it is essential to maintain a proactive and interdisciplinary approach, engage stakeholders, and foster dialogue to shape responsible and socially beneficial scientific practices.

Role and Evolution of ELSI Research

At its dawn in 1990, the report by the ELSI Working Group established the fundamental goals of the ELSI program, which included anticipating and managing the impacts of human genome mapping, investigating its ethical and legal consequences, encouraging public discourse, and formulating policies ensuring beneficial information use for individuals and society ("ELSI Planning and Evaluation History," 2012; "Ethical, Legal, and Social Issues Research Archive," 2023). Thus, ELSI has evolved to be an

interdisciplinary research field that explores how scientific advancements, such as genetic research, may impact society.

Since then, ELSI scholars have conducted numerous studies to explore issues in genetics and genomics research, both in basic science and clinical translation. They have also explored broader societal concerns related to emerging technologies in life sciences to engage with various stakeholders and employ diverse methodologies (Dolan et al., 2022). They have focused on identifying and addressing ethical and societal issues associated with scientific research to facilitate public discussion, ensure societal benefits, and mitigate potential harm.

The ELSI Program has impacted scientific and public policy on the conduct and implementation of genomic research and medicine by, for example, informing policies and governance mechanisms for biobanks, changing consent forms for genomic studies, and influencing intellectual property laws surrounding genomics (Parker et al., 2019). Furthermore, ELSI research programs have contributed to significant legislative and judicial outcomes. Concrete policy outcomes have been credited to them, including the Genetic Information Nondiscrimination Act, Universal Declaration on the Human Genome and Human Rights, improvements in consent forms and modalities for genomic studies, guidelines for data sharing, and governance models for biobanks (Caulfield et al., 2013; Collins, 2004; Dolan et al., 2022; McEwen et al., 2014; "NHGRI History and Timeline of Events," 2023; Wolf et al., 2008).

ELSI research is one approach for addressing specific ELSI issues, thus balancing the roles of facilitators and critical assessors (Oliver & McGuire, 2011), or, in other words, the role between 'moralisers' and 'smooth operators' in bioethics (Metzler, 2011). This role can be fulfilled by retrospectively assessing implications or by attempting to anticipate consequences to illustrate the path that genomic research should take (Dolan et al., 2022). Hence, ELSI research questions both sides of the classic divide between 'is' and 'ought.' Once a normative claim is developed, it is imperative to affect changes based on this norm, implying that when formulating a specific norm, ethicists should consider whether and how it can be enacted (Sisk et al., 2020). Formulating normative claims is the first step, and other challenges lie in translating these claims into tangible and effective policies. This endeavour embraces a spectrum of roles, ranging from facilitators to critical assessors, scrutinizing potential pitfalls. The interplay between these roles mirrors the broader discourse within bioethics, where the dichotomy between 'moralisers' and 'smooth operators' continues to shape the ethical landscape.

In conclusion, the role and evolution of ELSI research in genetics and genomics have impacted scientific practice, public policy, and ELSI research methods. ELSI scholars have diligently explored the implications of scientific research, engaging with stakeholders in proximity but also from a distance through diverse methodologies to facilitate public discussions on ELSI, promote societal benefits, and mitigate the potential harms of scientific advancements.

Methods of ELSI Research

ELSI research adopts a multidisciplinary approach to investigate the implications of scientific advancements in different academic disciplines such as ethics, law, philosophy, and social sciences (Ogbogu & Ahmed, 2022).

Earlier methods in empirical bioethics focused on philosophical analysis to inform and support decision-making in medicine and science (Schneider et al., 2021). Recent ELSI research has expanded its scope to study and anticipate the implications of research fields and has employed an array of methodologies, including empirical research methods. Empirical research involves observation and data collection, while nonempirical research involves philosophical and legal analysis and the methods of the humanities (Parker et al., 2019). ELSI research integrates the unique yet interconnected functions of empirical and non-empirical methods, encompassing both normative and conceptual research (Parker et al., 2019).

However, other questions can only be addressed partially or primarily by analysing data, as they delve into inquiries of value and meaning (Oliver & McGuire, 2011). These value-focused normative and meaning-focused conceptual questions require nonempirical research methods, including philosophical and legal analysis and the methods of the humanities (Oliver & McGuire, 2011).

The shift towards ‘empirical bioethics’ was enforced by recognising that stakeholders’ perspectives are crucial for producing practical ethical recommendations, enriching bioethics scholarship and

challenging researchers' viewpoints (Parsons et al., 2023). Additionally, debates on equal access to health services and the fair distribution of limited resources raised ethical considerations, and social changes led to an emancipatory movement for patients, challenging the traditional and/or paternalistic relationships in biomedical and clinical research (Borry et al., 2005).

However, to address the potential shortcomings of relying solely on research participants' views or existing literature introducing bias and subjectivity, the concept of ethno-immersion in bioethics research has emerged. Ethno-immersion develops a more nuanced understanding of the context, builds rapport with participants, and provides insights that might not be achievable through data generation alone (Parsons et al., 2023).

Moreover, technological advancements have opened new avenues for empirical bioethics research. Technologies and tools enable the investigation of how bioethical issues manifest in online spaces, providing researchers with valuable insights into the digital landscape and its impact on ethical considerations (Ogbogu & Ahmed, 2022; Schneider et al., 2021).

This integration of technology into ELSI research enriches the understanding and overall adoption of both empirical and nonempirical methods in ELSI research, allowing for explorations of the implications of scientific advancements. ELSI research has shifted its emphasis from theoretical exploration to a stronger focus on policy development (Joly et al., 2014). By combining various

methodological approaches and stakeholder engagement methods, researchers can identify potential ELSI, thereby contributing to informed decision-making in policy development for science and technology.

Stakeholder Engagement in ELSI Research

Bottom-up approaches to stakeholder engagement in genomics and policy development involve incorporating input from stakeholders at the grassroots level, including laypeople and scientists. This ensures that diverse perspectives are considered when developing policies or implementing programmes. A bottom-up approach to ethics in genomic research consists of a broad public engagement setting or mechanism to involve stakeholders ahead, thereby addressing difficulties that constrain open discussions on ethical issues (Felt et al., 2009). Through public engagement, ethical considerations can be addressed ahead of time, thus preventing difficulties that may arise from constrained discussions, and ensuring that the perspectives and concerns of all stakeholders are considered. In the context of genomic research, the shift from a top-down to a bottom-up model to address ethical aspects is supported by the current focus on participatory genomic research with a high degree of public engagement and democratised genomic science and, in parallel, deinstitutionalising science (Aungst et al., 2017). Thus, genomic technologies and data can be pulled out of the ivory tower and challenge conventional and often procedural genomic

research processes and norms by implementing participant-driven genomic research (PDGR), which aims to disrupt the hierarchies of scientific knowledge production, as well as update and democratise research governance, regulation mechanisms, and oversight mechanisms of ethical aspects in human genomic information management (McGowan et al., 2017). The democratising ethos behind stakeholder engagement in genomics opens up new possibilities for inclusive research and policy development; however, it also presents challenges concerning the allocation of responsibilities between researchers and participants (Aungst et al., 2017). This social dimension of research with stakeholders was also acknowledged for biobanks, where the connections and exchanges it establishes with various groups, encompass all facets related to ELSI that the biobank is accountable for (Bjugn & Casati, 2012; Lecaros, 2023).

Incorporating diverse perspectives through public and stakeholder engagement in genomic research and biobanks can lead to more inclusive policies; nevertheless, challenges remain and are further discussed in the following sections and the section on the `ELSI Framework of Biobanks`.

Navigating Criticism: Challenges and Debates in ELSI Research

Over the past 3 decades, criticisms of ELSI research have arisen; yet, they were also present early on because of the allocation of project funds to study the consequences and ethics of genomics, in the fear that it would invite public scrutiny (Dolan et al., 2022). Some researchers argue that ELSI researchers are compelled to act as intermediaries between science and the public, manufacturing acceptability for scientific endeavours, while others are concerned that ELSI research (and its funding) might divert attention from other scientific endeavours (Dolan et al., 2022). Other scholars argue that ELSI has not fulfilled the ambitious outcomes anticipated but has focused on areas that promote and enable scientific progress rather than setting constraints or raising critical issues (Yesley, 2008).

The literature presents mixed results, as defining the success of an ELSI project is a complex task. This is because challenges involve the clinical domain, professional culture, and personal preferences, with ELSI evidence sometimes perceived as anecdotal (Conley et al., 2020). The direct policy impact of ELSI research is also a subject of ongoing debate, with questions raised about the use of ‘speculative ethics’ in making policy recommendations and the limitations in real-life policy impacts (Conley et al., 2020; Dolan et al., 2022). This may partially stem from institutional and personal challenges such as value-laden epistemological differences between

the stakeholders involved in designing and conducting a genetic research study. In addition to epistemological differences, time constraints, knowledge gaps, and power imbalances have been identified as barriers to effective consideration of ELSI issues and their impact on policies (Balmer et al., 2015; Conley et al., 2020; Dolan et al., 2022; Seltzer et al., 2011). Furthermore, the methodologies employed in some ELSI research, particularly normative and conceptual analyses, remain relatively unfamiliar and opaque, particularly to researchers in the basic biomedical and translational sciences (Parker et al., 2019).

Moving forward, we will explore the role and evolution of informed consent in biobanks, elucidating the ethical foundations that have enabled biomedical and genomic research advancement. The use and standardisation of informed consent processes have enabled rapid advances in clinical and biomedical research over the last 100 years. However, their role and the type of data they allow for collection have changed (Dankar et al., 2019).

Role and Evolution of Informed Consent in Biobanks

Informed consent is a crucial component that has enabled the rapid progress of biomedical and genomic research; however, since its introduction, traditional forms of informed consent have been met with various criticisms. The informed consent form is an instrument that participants use to express their decision to participate in research. With this declaration, to be completed online or in paper

form, the participant confirms with a signature that they have been informed about and understood the conditions for participation in a study. Signing an informed consent form is necessary for their participation. Without consent, the researcher(s) cannot use a participant's data; thus, informed and voluntary consent must be obtained from research participants before the research begins (Calzolari et al., 2013).

The Nuremberg Act, established in 1947, introduced informed consent as a mandatory ethical and legal safeguard in the ethical research principles for human experimentation. This resulted from the Nuremberg Trials held after World War II to address unethical behaviour and the aim to address wrongdoing regarding medical ethics and human rights. The code was formulated by American judges addressing accusations that Nazi doctors had conducted murderous and torturous human experiments in the 'Doctors Trials' in concentration camps (Shuster, 1997; Tribunal, 1949). The Nuremberg Code was a significant milestone in developing ethical research principles and has influenced numerous international guidelines and regulations. The Nuremberg Act established that individuals must know the nature and purpose of the experiment, as well as the method, equipment, and practical aspects of the study (e.g. duration) before providing informed consent (Yaghoobi & Hosseini, 2021). Later, through the Helsinki Declaration, specifications about the expected risks and health effects were required. Then in 2008, considerations were added regarding the funding and financial context, advantages, possible conflicts of

interest, and intended benefits (Widdows & Cordell, 2011; Yaghoobi & Hosseini, 2021).

Figure 1 presents a comprehensive overview of the identified legal requirements of communication within the context of informed consent for a specific genetic research study to ensure compliance with legal standards and transparency.

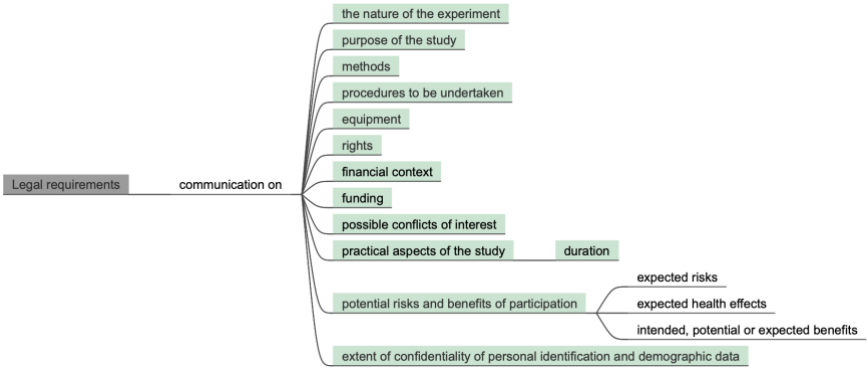


Figure 1: Overview of identified legal requirements for communication in informed consent for a specific genetic research study.

However, large-scale population studies and databases have challenged traditional conceptions of informed consent and raised specific concerns relevant to consent processes in this context (McGuire & Beskow, 2010; Teare et al., 2021). These arguments presented concerns in meeting the criteria of the 'right to withdraw', the fact that biobanks are research resources rather than research projects, and the future-oriented nature of biobanks highlighting their inability to adhere to the informed consent standards outlined in the Helsinki Declaration (Widdows & Cordell, 2011). These arguments collectively demonstrate the inherent difficulties of fully

informing participants and addressing the rights and interests of connected individuals in the context of biobanking.

The evolution of informed consent in biobanks reflects ongoing efforts to reconcile the principles of research ethics with the practical realities of large-scale data collection and storage. Reacting to criticisms or evolving needs, informed consent processes and modes have evolved; accordingly, various types of consent processes and models – from specific to broad, or from open and blanket to multilayered consent – have emerged (Fedeli et al., 2019; Salvaterra et al., 2008). Consequently, in the context of biobank research and whole-genome sequencing, innovative consent documents and procedures have been developed to address the unique nature of the long-term storage of biomaterials and data, which may be used for future unspecified and unforeseen research projects (Hirschberg et al., 2014).

However, despite its historical significance and legal foundations, informed consent faces criticism as the 'gold standard', as well as calls for evolution to ensure ethics in different biobank research settings. First, we discuss the legal requirements that validate the informed consent processes.

Revisiting the Role of Informed Consent in Research Ethics

To ensure ethical treatment, informed consent has long been the gold standard; however, scholars have questioned its suitability for ensuring ethics in research (Yaghoobi & Hosseini, 2021). Concerns

exist regarding the risk that biobank research policies will be superseded by the sum of informed consent provided for a given project, and that broad consent raises ethical concerns, even though the General Data Protection Regulation (GDPR) allows broad consent as a legal basis (Lecaros, 2023; Saunders et al., 2019; Soulier, 2019). Consent is necessary as a legal basis for data processing and for human experiments, but further consent is also used as a safeguard to allow ethical evaluation of the participation in research studies. Legal consent for data processing is governed by laws such as the GDPR, which requires specific, unambiguous, and freely given consent for processing personal data. On the other hand, legal consent for human experiments is guided by regulations such as the Declaration of Helsinki, which emphasizes voluntary informed consent, minimizing risks, and ensuring benefits to participants. Ethical discussions around consent for data processing or research experiments involve broader considerations, including the balance between individual autonomy and public interest, as well as the protection of privacy and confidentiality.

The ritualisation of consent as a formality may have helped to smooth over moments of dislocation in biomedicine, when responsiveness to ELSI concerns is limited to adapting the consent form (Am, 2019). Accordingly, consent might serve as an ‘empty signifier’ as a ritualised answer to clinical and medical research and ethics needs (Hoeyer & Hogle, 2014). Underpinning lies the assumption that informed consent procedures protect rights by

offering choices to the autonomous and informed individual and act as a counterposition to medical paternalism (Corrigan, 2003). Further problems have been identified regarding 'empty ethics', which lack social contextualisation or over-emphasise the paternalistic approach because of obvious limits to informed consent's processes and role (Corrigan, 2003; Hoeyer & Hogle, 2014).

However, the evolution of consent models has implicitly and explicitly focused on considerations regarding the principle of nonmaleficence when dealing with patients, but they have not evolved to account for the ethical obligation to comfort nonpatients as participants in biobanking or genomic screening research (Elton, 2021).

From an ethical and societal perspective, dealing with genetic information and large-scale population studies is complicated by issues such as the inappropriateness of informed consent in biobanking and the potential ignorance of the rights and interests of connected individuals (Widdows & Cordell, 2011). Among the voiced concerns is the relationship between autonomy, ignorance, and lack of prevention, possibly invalidating consent (Keren & Lev, 2022). This aligns with empirical studies on informed consent, where the recognition of relational autonomy, and science and technology studies (STS) on biomedicalisation, test, question, or refuse individual informed consent as the primary approach for respecting autonomy as a guiding principle (Felt et al., 2009).

Furthermore, many scholars have highlighted how informed consent is not suitable or appropriate in the era of WGS (Ebbesen & Sundby, 2015; Kronenthal et al., 2012). Investigations have confirmed that informed consent processes in the biobanking research context may miss some of the requirements because participants or patients are not appropriately informed, do not understand all information, or relevant information is lacking; thus, there is a lack of assurance that participants or patients can make free and informed choices in biomedical research contexts (De Sutter et al., 2020; Nathe & Krakow, 2019; Pietrzykowski & Smilowska, 2021; Utz et al., 2019). Furthermore, how the right to withdraw from research and research studies is implemented and respected might need to be clarified (Widdows & Cordell, 2011; Yaghoobi & Hosseini, 2021).

Accordingly, scholars have called for a broader conceptualisation of reciprocity in this context, as the alliance includes researchers, individual participants, and society as a whole (Fedeli et al., 2019; Sanchini et al., 2016). A discussion is required on whether individual consent is sufficient, if any form of collective consent should be developed and implemented, and whether researchers must obtain informed consent from both individual subjects and the collective needs to be addressed (Greely, 2001). The concept of "collective consent" in biobanks, genetic research, and other clinical contexts is an evolving area based on the idea of obtaining consent from a community or group rather than from individual participants and is particularly relevant when dealing with vulnerable or minority groups (Galasso & Geiger, 2023).

One strategy for addressing some ELSI concerns regarding consent is to create more sophisticated forms, such as dynamic consent (Biasiotto et al., 2021; Budin-Ljosne et al., 2017; Teare et al., 2021). Furthermore, the development of electronic informed consent allows for enhanced provision of additional information on specific parts of the research. Scholars have highlighted that it cannot replace human connections, but offers more advantages by being a more participant-centric solution (Yusof et al., 2022). While providing individuals with increased control and rights over their contributions represents a strong argument for dynamic interactive consent, the assumption that empowering and engaging people in biobanks through dynamic consent can be questioned, because biomedical research focuses on future health benefits; thus, the justification for active engagement and participation is less apparent (Steinsbekk et al., 2013).

Even if innovative technologies or methods increase participants' 'control' over decisions on samples and data, other fundamental issues exist about the validity of informed consent in research in and with biobanks that will be further discussed in the next sections. In summary, conventional ethical safeguards, such as informed consent, must be revised for the governance of biobanks. Therefore, novel ethical structures and frameworks continue to address issues related to the inadequacy of informed consent for biobanks, overlooking the rights and interests of interconnected individuals, the inhibition of information disclosure due to the prospective nature

of biobanks, difficulties in fulfilling criteria for the right to withdraw, confidentiality concerns, and ethical considerations regarding property, profit, and recontact (Lecaros, 2023; Widdows & Cordell, 2011).

Requirements for valid informed consent.

All study participants have legal rights. Participants use the informed consent form to express their decisions on how to participate. In genetic research, it is crucial that participants make informed decisions about whether to participate because there are implications for their participation. Informed, voluntary, and valid consent is a fundamental requirement outlined in numerous national and international guidelines and legislation (Capron, 2008; Hirschberg et al., 2014).

Accordingly, valid informed consent needs to fulfil various requirements, such as no coercion or other dynamics that could affect voluntary choices and that the prospective participant has been provided with the necessary information and has the capacity to express a choice (Resnik, 2021). Regardless of the different consent models, the essential elements that render consent valid are comprehension or understanding, voluntary participation, competence, and disclosure (Bromwich & Millum, 2021; Dougherty, 2020; Millum & Bromwich, 2021).

To make an informed decision, participants must be provided with sufficient information about the study, including its purpose,

procedures, potential risks and benefits, and their rights. To address this issue, researchers can provide educational materials, offer genetic counselling, allow sufficient time for participants to review the materials and ask questions, and use plain language summaries to present essential information, among other actions. An informed decision is made by a person who understands the nature of a particular situation, has been provided with sufficient information about the study, and has had the opportunity to ask questions and receive answers before deciding whether to participate. However, there are significant differences in how research guidelines shape informed consent processes in terms of their thoroughness, level of detail, and clarity in addressing issues relevant to biobank consent procedures (Hirschberg et al., 2014). For example, consent processes in German biobanks were found to exhibit varying levels of adherence to 'soft law' components and ethical guidelines in their consent forms, with most forms lacking necessary information (Schaar, 2017).

In the next sections, we will further discuss the implications of such findings on the validity of informed consent for this context.

Validating Consent in Research: The Shifting Perspectives from Aspiration to Requirement in the Consent Comprehension Debate.

Participants should understand the information provided and make voluntary decisions to participate. However, a consensus is yet to be reached on whether it is necessary, how to measure it, and what to

do about a potential lack thereof. The lack thereof, or ways to investigate ‘the understanding of the understanding’, is one of the central critiques of ethical and legal scholars (Beskow et al., 2017; Beskow & Weinfurt, 2019).

Moreover, the question of whether consent comprehension should be an ethical requirement or an ethical aspiration, remains a subject of debate. This raises critical considerations about the responsibility of researchers and study policies to ensure participants’ understanding. Without a ‘threshold of understanding’ from the participants’ perspective, ethical challenges arise in determining how study policies should navigate this issue (Beskow & Weinfurt, 2019; Hendriks et al., 2019). Ergo, without clarity on this issue and potential solutions for assessing the understanding, consent may not be valid because respect for participants as autonomous agents requires a robust understanding of the study and its implications on their side (Dougherty, 2020). To address this matter, Bhutta (2004) proposed a distinction between 'informed' and 'understood' consent. While discussions on whether consent can be invalid under the disclosure and understanding of requirements continue, empirical work can illustrate how to address ethical concerns and more accurately define what needs to be disclosed and understood (Bromwich & Millum, 2021; Millum & Bromwich, 2021). However, some scholars argue that the strategy of disclosing all information or using neutral frames to evoke an autonomous choice may not validate consent in this context (Chwang, 2016).

In the following section, we briefly introduce frames, framing and how they might affect the discussion on valid informed consent in this context.

Exploring Framing Effects and the Validity of Informed Consent.

The concept of framing effects was initially introduced by Amos Tversky and Daniel Kahneman, who demonstrated that individuals may express different preferences towards the same option based solely on how information about an option is framed (Tversky & Kahneman, 1981). Although the recognition of framing effects is relatively well-established in academic psychology, its moral significance in the context of informed consent in medical research has only been a subject of recent exploration in the field of ethics.

Framing effects have been observed to influence various decisions and risk assessments in individuals' consenting processes, raising concerns about the validity and ethical implications of such consent. This is because the strategy of disclosing all frames or using neutral ones may not suffice to validate consent in the medical context (Chwang, 2016; Iltis, 2006). Furthermore, providing participants 'with both sides of the story' (Faden, 1986) to prevent framing-related effects or concerns may sometimes be impractical (Hanna, 2011). Strategies exist for eliminating or debiasing framing effects from cognitive psychology by ensuring that the subject's decision remains consistent regardless of how the information is presented or framed (Chwang, 2016).

Moreover, scientific experts hold a privileged position in policy-making, influencing the framing of issues ‘scientistically’ or have the authority regarding ‘appropriate simplification’; thus, problems became narrowly or technically framed as ethical issues while excluding broader considerations (Hilgartner, 2016; Irwin, 2001; Moore, 2010).

As one delves deeper into the intricacies of ELSI in this context, it becomes evident that safeguarding the validity of consent requires thoughtful consideration to address potential biases and skewed information frames. These biases and skewed frames arise from the framing of protecting the autonomy and well-being of the study participants through information provision and informed consent processes.

Recall by Genotype

The overarching aim of this chapter is to delve into the multifaceted dimensions of Recall-by-genotype (RbG) studies, its scientific utility and its distinctive ELSI. The sections include an introduction to the scientific utility underpinning RbG and how RbG studies hold promise for advancing precision medicine goals. We then delve into practical aspects and ELSI related to classifying or categorising participants into smaller subgroups, the critical aspects of recall (recruitment, reinvitation) strategies, and the unique challenges surrounding informed consent for RbG studies. The last section introduces the decisive aspects of disclosure, communication strategies, and policies for RbG studies and offers insights into ethical considerations.

The Scientific Utility of RbG Studies

Advancements in genomic research have led to the generation of vast amounts of genetic information, presenting both opportunities and challenges in the realm of biomedical and genetic studies. Excess genetic data generated by various studies are often left unused because of the lack of appropriate bottom-up models for recalling and performing additional hypothesis-driven investigations with participants in large-scale biomedical or genetic research (McGuire & McGuire, 2008). In response to this limitation, RbG approaches – as bottom-up approaches – have emerged as a

solution that can utilise already collected genetic data and potentially enhance the utility of genomic cohort studies. Enabling bottom-up approaches to genomic cohort studies and nested follow-up studies may significantly improve the evolution of human genetic research because of the ability to investigate specific participants with specific preconditions, thereby studying the functional significance of genetic variation in the human population (McGuire & McGuire, 2008).

RbG approaches can overcome this limitation by identifying and recalling participants through their personal genotypic information and performing further studies. This recruitment for follow-up studies with tailored examinations allows for detailed phenotyping of a subgroup with a smaller sample size. This can be termed 'targeted phenotyping', as it represents a possibility to maximise the utility of generated genetic data (McGuire & McGuire, 2008).

From a scientific perspective, RbG strategies are particularly useful for identifying causal relationships between genes and diseases as well as discovering underlying disease mechanisms and genetic associations; this is especially the case when rare genotypes are involved and extensive sampling and phenotyping would be costly (Corbin et al., 2018; Franks & Timpson, 2018; Momozawa & Mizukami, 2021). A review of RbG approaches for complex cardiometabolic traits reported that most earlier RbG studies predominantly employed descriptive approaches and adopted targeted recall strategies to reduce the necessary sample size for implementing phenotyping methods (Franks & Timpson, 2018).

RbG approaches are not universally applicable to all studies, and their suitability depends on factors such as the nature of the genetic variation and its thorough characterisation (Corbin et al., 2018). RbG designs have provided insights into causal biomarkers and ascertained genetic causes, increased the understanding of biological mechanisms underlying genetic associations, and identified prodromal and potentially modifiable risk factors (Alver et al., 2019; Corbin et al., 2018; Kavanagh et al., 2010). Furthermore, these approaches are used to increase the statistical power and precision of genetic association studies, and can be particularly useful for studying rare genetic variations that may be difficult to identify through other means (Corbin et al., 2017; Momozawa & Mizukami, 2021).

To maximise the utility of RbG studies, it is necessary to combine them with population- and patient-based data records of genotypic variation (Corbin et al., 2018).

There are potential benefits to RbG approaches due to recalling individuals with specific genetic variations, such as the potential to reduce bias and improve the generalisability of research findings (Taylor et al., 2017). Furthermore, the sample sizes for case-control comparisons in RbG studies are smaller than in random sampling studies; consequently, detailed phenotyping is more cost-effective and has higher statistical efficiency compared with other study designs (Corbin et al., 2018; Corbin et al., 2017). Moreover, RbG sampling strategies have two significant advantages over the traditional observational epidemiology. First, by using Mendelian

randomisation (MR), which arises from the random allocation of alleles at conception, these strategies enhance the ability to draw causal inferences in population-based studies while minimising issues in observational studies (Burgess et al., 2015; Corbin et al., 2018; Davey Smith & Hemani, 2014; Smith & Ebrahim, 2003). Second, by focusing phenotypic assessments on carefully selected population subgroups, insights into the mechanism and the aetiology of health outcomes can be improved in a cost-efficient manner through the targeted deployment of more precise and informative phenotyping across already known biological gradients (Corbin et al., 2018; Lawlor et al., 2008).

Different RbG approaches can be used to investigate single variants (RbGsv) and multiple variants (RbGmv). RbGsv studies aim to understand biological pathways using specific loci by defining strata based on a single genetic variant and then further examining these samples or participants for phenotypic analyses (Corbin et al., 2018). The sampling strategy for RbGsv depends on the characteristics of the genetic target variant and the hypothesis regarding the mode of inheritance (Corbin et al., 2018). The chosen variants may induce a direct biological change or have predicted effects, providing natural experiments that can yield information about the specific role of biological pathways and potentially inform about the safety and efficacy of medicines (Corbin et al., 2018; Lee et al., 2016).

By contrast, RbGmv studies use multiple genetic variants to design studies focused on the impact of an exposure of interest, selecting

variants that serve as a dependable proxy for the exposure (Corbin et al., 2018). Accordingly, the selection of genetic variants depends on the ability of variations in genotype to serve as a dependable proxy for the exposure of interest. This approach generates comparison groups that are small enough for a detailed examination while improving the accuracy of the causal estimate compared with estimates derived from individual genetic variants, with a genetic risk score used for further analysis (Corbin et al., 2018). After the genetic risk score has been constructed within the RbG sample, individuals are ranked based on this score, which is then used for further analysis.

Rather than recruiting rare mutations of significant impact in a balanced manner, the RbGmv technique generates comparison groups that are small enough for a detailed examination while ensuring that the exposure gradient for the risk factor is just as pronounced and influential as it would be in an analysis of the entire population sample (Corbin et al., 2018). Using multiple genetic variants in this manner can improve the accuracy of the causal estimate compared with estimates derived from individual genetic variants (Corbin et al., 2018). However, RbGmv approaches usually characterise heterogeneous biological processes. Because each participant carries a unique set of alleles, they are not meant to be used for identifying specific biological perturbations in this context (Franks & Timpson, 2018).

Advancing Precision Medicine Goals Through RbG Studies

The postgenomic narrative of integrating precision medicine into health care to provide 'genotype-informed', 'gene-specific', and 'genome-driven' diagnoses' as well as 'genotype-specific treatment choices' demands unprecedented amounts of assembled biological samples and genetic and clinical data as well as a deep understanding of genotype–phenotype interactions (Bruggemann & Klein, 2019; Khordad & Mercer, 2017; Kumar, 2020). Similarly, the prospect of employing precision medicine in the healthcare sector demands a deep understanding of said interactions (Bruggemann & Klein, 2019; Klein et al., 2007; Prasuhn & Bruggemann, 2021).

Accurate and reliable phenotype descriptions are required to associate specific traits and illnesses. To ensure reliable phenotype descriptions, statistical models require different types of data and information from specific participants with the variant versus those without it. To date, detailed phenotyping methods for increasing the understanding of an individual's phenotype have not been given the attention they deserve, yet their popularity in biobanks will only increase (Corbin et al., 2018; Founti et al., 2009). Furthermore, the use of RbG approaches and studies will increase because of the availability of individuals' genetic information from healthcare and research and through direct-to-consumer genetic testing companies (Budin-Ljosne et al., 2013).

The current use of RbG studies primarily involves follow-up studies that use previously collected genetic information (Beskow et al.,

2012; Beskow et al., 2010; Beskow et al., 2011; Budin-Ljosne et al., 2013; Cadigan et al., 2011; McGuire & McGuire, 2008; Michie et al., 2012; Tabor et al., 2011). As genotyping becomes more affordable, the use of RbG studies is expected to expand for the following two main reasons (Budin-Ljosne et al., 2013):

1. Recruitment Through Health Care Systems: With the increasing availability of genetic information in healthcare databases, individuals may be recruited into RbG studies based on their genetic data to offer enhanced disease diagnosis, therapy, and clinical outcomes through integrated analyses of clinical, biological, environmental, and genetic data (Budin-Ljosne et al., 2013). Large-scale databases with linkable electronic health records (EHRs) will be valuable resources for conducting RbG studies, particularly for advancing precision medicine goals; moreover, as access procedures and requirements for these databases are established, RbG studies are expected to be in high demand (Budin-Ljosne et al., 2013; Council, 2011; Olson, 2017).

2. Genetic Data from direct-to-consumer Companies: The emergence of private companies that offer affordable genetic screening services to consumers has led to the accumulation of vast genetic datasets, and the volume of research on rare genotype–phenotype combinations has increased (Budin-Ljosne et al., 2013).

In summary, RbG studies represent a valuable study design that leverages existing genetic data to inform participant selection for further investigation. However, the peculiarities of the RbG design

and the different approaches also raise concerns regarding ELSI, which are further discussed in the next section.

Overview of ELSI of RbG Studies

RbG studies have a nested substudy characteristic that necessitates a comprehensive assessment of the specific substudy and the original cohort study. Some ELSI stemming from study design characteristics are related to or can only be assessed and addressed in conjunction with the original cohort study.

This inherent design complexity raises peculiar ethical questions that demand a more tailored ELSI evaluation, one focused on the interactions and implications at both the micro and macro levels. The following sections provide a short overview of the different ELSI of RbG, but further in-depth considerations on the ELSI of RbG approaches are extensively discussed in Chapter 1.

Recruitment, Reinvitation, or Recall

One of the main differences between RbG studies and other genetic research studies is the recruitment, which uses a recall strategy. Unlike other genetic research studies, RbG studies make the participant`s genotype the primary factor determining their eligibility for the study. Genetic information that has already been collected from previous research studies, medical records, or biobanks is used to identify individuals with specific genotypes of interest. The process of recalling research participants presents

challenges to the established ELSI framework, some of which are akin to those encountered when dealing with the return of unsolicited findings from Whole-Genome-Sequencing (WGS) (Minion et al., 2018).

Another ELSI concern revolves around the potential for participants to draw incorrect conclusions with each interaction regarding the selection of their specimens for specific RbG studies. Participants might misunderstand the reasons behind the selection of their specimens, leading to misconceptions about the research objectives or potential implications for their health and well-being (Beskow & Dean, 2008; Haga & Beskow, 2008; McGuire & Beskow, 2010).

Furthermore, RbG studies often rely on a family based approach that requires identifying, matching, and recruiting or recalling family members for research studies. Different recall strategies involve different levels of concern about privacy, how to minimise the potential privacy invasion, confidentiality, and participant accrual to provide an unbiased and informed sample (Beskow et al., 2004).

Classification into smaller subgroups.

The recruitment in RbG studies recalls eligible participants as either carriers or controls. This is heavily affected by how the relationship between the participants of the original cohort study and the researchers was formed.

While researchers recruit potential prospective participants with genetic variants or characteristics of interest, they may or may not have any phenotypic conditions associated with the genetic variants or diseases being investigated in the study. Individuals who are unable to experience a disease condition may find being invited to participate in a study that investigates a specific genetic variant likely associated or certainly associated with a specific disease to be confusing or even worrisome (Beskow & Dean, 2008; Beskow et al., 2010; McGuire & McGuire, 2008; Michie et al., 2012).

Informed Consent for RbG Studies

Specific considerations must be made in terms of the informed consent processes to provide choices on whether study participants receive or do not receive individual research results (Amendola et al., 2015; Mascalzoni et al., 2021; Papaz et al., 2019; Patch & Middleton, 2018; Thorogood et al., 2019). The provision for recalling participants lies in the nature, consent, and context of the original study (Beskow et al., 2012; Beskow et al., 2011; Corbin et al., 2018). Some original studies have not obtained explicit informed consent to recall participants by genotype (Franks & Timpson, 2018). Furthermore, some scholars have argued that it is unacceptable to recall participants (Mascalzoni et al., 2021) because of ethical concerns due to the risk of violating the individual's privacy and right not to know because some genetic information is implicitly disclosed (Beskow et al., 2004; Beskow et al., 2010;

Beskow et al., 2011). Moreover, the scopes of RbG studies may deviate from the communicated initial and consented scopes of the cohort study, for which the consent was obtained. This raises the question of whether reconsent is necessary before recalling and inviting participants to an RbG study and whether recontacting participants for reconsent to a study was included in the original consent form.

Furthermore, it is crucial to view and design informed consent not as a one-time event but as an evolving process in which participants' choices may change over time (Michie et al., 2012). This is also critical for providing the research institute or biobank with the possibility of including new study designs, such as RbG, with physical recall studies or based on the re-use of data in the consent processes.

Return of Research Results

In RbG studies, there are two potential moments at which research results can or may be returned. The first one is the research results from the previous study as the reason for eligibility that is disclosed in the recall and invitation phase. The second is during or after the specific RbG study and concerns the results of the specific RbG study rationale.

In designing an RbG study process, the obligation or lack thereof to return individual research results to study participants should be

considered upfront (Beskow et al., 2012; Mascalzoni et al., 2021). We will deepen the discussion on whether, how, and when the ethical obligation to communicate and disclose individual research results in the next section and then discuss the implications in the discussion.

Disclosure & Communication Strategy

In this context, disclosure refers to the act of informing participants of their genetic information and the associated risks or more general implications (Mascalzoni et al., 2021; Minion et al., 2018). Designing genetic information disclosure strategies in RbG studies can be challenging for researchers or other responsible entities, as they must balance their duty to provide information on the scientific rationale for recall, with the right of the study participants not knowing sensitive information.

Considerations that Shape Disclosure Policies and Communication Strategies.

Sharing information may pose ELSI dilemmas even if no direct or explicit disclosure occurs. In an RbG study, disclosure can or may occur in the recall phase because of the provision of information about the study design, genetic variants of interest, and associated diseases. Accordingly, the invitation of prospective participants to an RbG study may have already disclosed sensitive genetic

information in the form of information on potential disease risk or previously unknown or unwanted personal genetic information.

Every research study policy situates itself somewhere between two opposing positions on the disclosure of research results. The two positions are ‘complete nondisclosure’ and ‘complete full disclosure’ (Pont-Sunyer et al., 2015). Both positions significantly affect the study design, the interaction with participants, and the participants themselves. Nondisclosure inhibits communication, even in life-threatening situations, and full disclosure might be difficult to provide because of the dynamic nature of scientific advances (Pont-Sunyer et al., 2015).

Arguments exist for being restrictive and supporting a nondisclosure policy, ranging from not diverting resources from the core research activities to the premature condition of not being sufficient to translate group-based research into individualised information (Christenhusz et al., 2013; Solberg & Steinsbekk, 2012; Steinsbekk et al., 2013). Studies based on stakeholder perspectives on the return of individual research results from genomic research have expressed a high level of interest, whereas those responsible for providing the results have tended to approach it cautiously (Vears et al., 2021). It must be kept in mind that in the research context, a returned result will mostly be ‘positive’ in terms of identifying a cause, because it is unlikely that participants will be informed that nothing has been found (Vears et al., 2021).

In this context, a genetic study by Pont-Sunyer et al. (2015) on PD caused by LRRK2 mutations suggested a qualified disclosure policy, because the return of research results is less straightforward. If participants wished to receive individual research results, they were required to be well informed about the meaning of the results for themselves and their families (Pont-Sunyer et al., 2015). The same study illustrated the differences and variations in policies regarding the disclosure of research results, for example, whether confirmation by a certified laboratory is required and whether disclosure is mandatory for different groups of subjects, reflecting differences in national laws.

For example, in the Bristol-based Avon Longitudinal Study of Parents and Children (ALSPAC), using RbG research presented a challenge for ethical conduct. This is because the researchers had to deviate from existing policies of the nondisclosure of results and risk unanticipated harm or mask the full structure of the study design, thereby missing an opportunity to open a process of disclosure within genotype-directed research (Minion et al., 2018). ALSPAC's Ethics and Law Committee drafted a policy regarding disclosing biomedical information to participants, which stated a general rule not to disclose biomedical information to cohort participants unless the benefits outweigh the risks, and specific conditions are met (Committee, 2018; Minion et al., 2018). Accordingly, the researchers and information materials did not communicate the particular genetic variation(s) to potential participants when recalling and conducting an RbG study (Minion et al., 2018).

In addition, scholars have discussed the principles of respect, reciprocity, beneficence, and justice, hinting at the duty of offering research results to participants.

Some have raised concerns about whether these principles are upheld through disclosure or infringed upon by non-disclosure. They also questioned whether the communication of individual research findings aligns with the ethically significant distinctions between research procedures and clinical care, raising concerns over whether research can and should serve clinical purposes (Miller et al., 2008). Furthermore, partial disclosure in the recall phase may blur the lines between research and clinical services. This 'hybrid state' created through the disclosure of research results that are perceived to have some clinical utility may result in inadequate ethical research practices (Miller et al., 2008). In the research context, the primary aim is to address the research question, thereby generating knowledge or insights into the issue at hand, and only a secondary purpose to provide results to guide clinical care may exist (Hayes, 2011; Vears et al., 2021). However, others have argued that drawing a distinct boundary between research and clinical contexts is inappropriate in translational genomics, while there may be overlap, which may help explore the issues separately (Angrist & Jamal, 2015; Berrios et al., 2018; Vears et al., 2021; Wolf et al., 2018).

Notably, the entire disclosure of individual research results might be beneficial as it respects participants' autonomy, promotes transparency, and allows individuals to make informed decisions

about their health. However, the decision for a full disclosure policy for an RbG study has economic implications, such as the cost of returning results and the potential burden on healthcare systems. Furthermore, full disclosure might be difficult because of the dynamic nature of scientific advances (Pont-Sunyer et al., 2015).

By contrast, total nondisclosure avoids the costs of translating the results for individual participants and result disclosure. The main argument for a non or restricted disclosure policy is to avoid or prevent harm (Pont-Sunyer et al., 2015). However, it raises ethical concerns, such as a lack of transparency and participants being deprived of potentially valuable health information. Therefore, finding a middle ground that considers both economic feasibility and ethical considerations is crucial for disclosure policies in RbG studies.

The Cooperative Health Research in South Tyrol Study & Biobank

This chapter will illustrate the study context related to Cooperative Health Research in South Tyrol (CHRIS) and the linked biobank. Commencing with an introduction to the CHRIS Study and the broader concept of biobanks, we progressively delve into the historical evolution of biobanks and the associated ELSI. Subsequently, we explore the specific ELSI framework for biobanks in Italy, closely examining the CHRIS Study's legal foundation. This is followed by a section on the dynamic informed consent framework employed within the CHRIS Study and its pivotal role in decisions related to the return of research results to participants. Further, we will explore the overarching rationale behind the RbG approach in the CHRIS and Protectmove Study linked to considerations on the feasibility assessment. We then present the test case, leading to an in-depth examination of the disclosure and communication strategy tailored for the CHRIS RbG study. The chapter concludes with an overview of the legal framework governing disclosure and the return of research results at the international and Italian levels.

Introduction to Biobanks

Biobanks are repositories for biological materials and biospecimens, such as blood, tissue, and DNA, as well as associated data, such as health information, which can be used in medical research

(Annaratone et al., 2021). Biobanks are an essential resource for research in various fields, including medicine, genomics, proteomics, and bioinformatics. Their establishment and management require the careful consideration of several factors, including accreditation, informed consent, ethical and legal considerations, standard operating procedures (SOPs), personnel considerations, biosafety requirements, equipment and space considerations, IT, and other factors such as funding and sustainability (Harati et al., 2019; Paskal et al., 2018; Sotelo et al., 2021).

These repositories can be broadly classified as public, private, or academic and exhibit diverse scales and scopes, ranging from local to national and international (Paskal et al., 2018; Sotelo et al., 2021). While the majority of biobanks are in North America and Europe, most countries worldwide have demonstrated significant dedication to establishing and expanding biobanks as research resources for various purposes (Chen & Pang, 2015; Klingstrom, 2013; Lawlor et al., 2013; Meslin & Goodman, 2009; Scott et al., 2012; Sgaier et al., 2007; Vaught et al., 2014).

The characteristics and functionalities of biobanks are highly diverse, primarily influenced by their specific scientific focus. The aspects and characteristics of different repositories and biobanks vary but can broadly be classified. This classification is based on their intended use of data and information (e.g., teaching, research, personalised medicine, or epidemiological studies), types of samples collected (e.g., human, animal, or plant), funding models

(i.e., public, social, or private), processes (e.g., biological and bioinformatics), participation and access (i.e., private or public), whether they are population-based or disease-oriented, and the type of medium which can be physical or virtual (Paskal et al., 2018; Sotelo et al., 2021). Additionally, biobanks exhibit varied organisational structures, ranging from individual biobanks to interconnected networks and centres of expertise, each with distinctive governance types (Sotelo et al., 2021).

Brief History of the Evolution of Biobanks

While the history of biobanks dates back to the early days of human genetics research, the rise of large-scale genomic biobanks and their equivalents is a relatively recent development; between 1980 and 1999, the number of biobanks increased significantly (Greely, 2007; Yaghoobi & Hosseini, 2021). As part of its '10 Ideas Changing the World Right Now' series, Time magazine highlighted biobanks in 2009 ("10 Ideas Changing the World Right Now - TIME," 2009). Also in 2009, the Organisation for Economic Cooperation and Development published impactful guidelines on human biobanks and genetic databases that outlined the following broad definition: *'[H]uman biobanks and genetic research databases [are] organised as repositories utilised for genetic research, comprising human biological materials and/or data obtained from their analysis, along with associated data*' (Lecaros, 2023, p. 282). Then, in 2012 the European Commission provided further clarification by identifying

and addressing the ethical and regulatory challenges through an expert group report and recommendations (Innovation, 2012).

Notably, the research environment has changed due to new sophisticated genetic and genomic technologies, the advancement of databases containing large amounts of data, and the widespread data sharing among national and international institutions (Bledsoe, 2017). Technological advances have enabled and driven the collection, analysis, and sharing of large amounts of genetic and other types of health- and lifestyle-data. The growing need for cross-border data sharing emphasises the significance of aligning and harmonising legal and other frameworks to create a unified landscape for personal data protection throughout the EU (Penasa & Tomasi, 2021; Piciocchi et al., 2018).

The Global Alliance for Genomics and Health developed a framework, published in 2014 and reaffirmed in 2019, for addressing proposals for a global governance framework that prioritises privacy and confidentiality, transparent sharing of samples and data, and equitable distribution of benefits ("Framework for Responsible Sharing of Genomic and Health-Related Data," 2023). Its foundational principles facilitate compliance with the obligations and norms set by international and national law and policies while the core elements should be interpreted to acknowledge different levels of risk and community cultural practices. However, research in biobanks is still far from harmonising and standardising some aspects, such as ethical and regulatory standards, both nationally and internationally (Caenazzo

& Tozzo, 2020). European research infrastructures, such as BBMRI-ERIC and ELIXIR, uniquely bridge national infrastructures and resources, providing a framework for transnational collaboration and data pooling (Saunders et al., 2019). This infrastructure can serve as a model for an international federation by adhering to global standards and maintaining international collaborations. Navigating the intricate landscape of biobank research and its ELSI is a multifaceted challenge that will be further discussed in the next sections.

ELSI Frameworks and Challenges for Biobanks

Legal regulations must guide concrete development while not limiting the freedom of research. They must also promote and ensure respect for the rights of subjects who decide to donate their samples or participate in studies, as well as the rights of the researchers and institutions wishing to use them (Cannovo et al., 2020; Fedeli et al., 2019).

The Medical Declaration of Helsinki, the most significant code, has been adopted by the World Medical Association (Association., 2001). While it was initially designed for medical research, its rules and concepts have been helpful in other research areas, which has contributed to its central position in research ethics in biobanks. However, a code is not a legal document, and legislation has entered the field of research ethics with laws.

Even though the GDPR provides a legal framework for protecting personal data, it presents challenges when applied to health research and biobanking activities, as the GDPR does not explicitly address them (Cippitani et al., 2022). These include the secondary use of data collected for other purposes, the need for broad consent to ensure the use of data/material in subsequent research activities (Hallinan, 2020), the use of historical collections without prior informed consent (Cippitani & Colcelli, 2021), the unique nature of 'genetic data' (Cippitani, 2018), and the uncertainty surrounding the rights of donors and the withdrawal of consent (Cippitani et al., 2022).

Furthermore, the ethical landscape is changing rapidly as many countries have made significant efforts to establish biobanks, despite some possibly lacking adequate legislation or governance frameworks (Chen & Pang, 2015; Klingstrom, 2013; Lawlor et al., 2013; Meslin & Goodman, 2009; Scott et al., 2012; Sgaier et al., 2007; Vaught et al., 2014). This lack has led to criticisms of biobanks for not being representative of the entire population and disproportionately benefitting specific groups, thus increasing health inequity (Bustamante et al., 2011; Chen & Pang, 2015; Daar et al., 2002; Hardy et al., 2008).

Moreover, biobanks have been recognised as ethically problematic because of the large amount of data that could be misused, potentially leading to discrimination, stigmatisation, and psychological stress (Artizzu, 2008; Greely, 2007). Furthermore, other issues concern information being collected and stored while

protecting the rights of the donor and providing access to data and relevant health results (including incidental findings) to enable the sound disclosure of results while protecting confidentiality; thus, data security measures and data protection have been added to evolving ELSI discussions for the biobanks of the future (Lecaros, 2023; Nicolás Jiménez, 2023).

The current era of abundant personal, demographic, health, and genomic data, coupled with artificial intelligence, presents opportunities for efficient and accurate research; however, the secondary uses of data for new research also introduce new ethical challenges, where it is essential to uphold and respect the principles of justice, beneficence, transparency, and respect for individuals to ensure responsible research practices (Bledsoe, 2017; Lecaros, 2023). As the number of samples and associated data increase, the risk of the reidentification of individuals also increases. This makes it increasingly difficult to guarantee anonymity because the potential for anonymous datasets to be reidentified when merged with other data sources and through the ease of data flow is facilitated by digital technologies (Teare et al., 2021). Therefore, it is critical for biobanks to use state-of-the-art security and encryption methods to protect data, thereby protecting the participant from adverse effects of participation (Gille et al., 2020). However, the advancement of big data analysis in public health poses challenges to existing regulations and standards that were established when the technology was less advanced (Schneider et al., 2021; Vayena, 2015).

On the other hand, complete data anonymisation would impede any potential individual benefits, such as the possibility of receiving the individual results of the research (Lecaros, 2023; Thorogood et al., 2019). Identifying a subject in legal terms requires the consideration of the reasonableness of the effort needed to accomplish such an operation; in this regard, it must be kept in mind that the concept is relative based on the context (Lecaros, 2023). For decades, the practice of using specimens and data for various projects without specific consent was accepted by experts because of the justification that the data were anonymised; however, this seems increasingly inaccurate and less accepted by participants (Dresser, 2014).

A significant apprehension in biobank governance models pertains to privacy issues, particularly regarding secondary uses. If not adequately addressed, these concerns could erode the trust of participants and society (Graziadei, 2022). Another major concerning ELSI is the potential for the misuse of data. Genetic information could be used to discriminate against individuals in areas such as employment or insurance (Cannovo et al., 2020; Cannovo et al., 2010).

Accreditation is another necessary foundation in order to ensure that a biobank meets certain quality, safety, and ethical standards, as they are essential for the credibility of the biobank and the trust of donors and users of the biological materials and associated data. Accreditation can be obtained from various organisations and involves a rigorous evaluation of the biobank's policies, procedures, and practices and compliance with local and national regulations

and ethical standards (Harati et al., 2019). Globally and within individual countries, a significant gap persists in adopting unified best practices, ethical and regulatory standards, and harmonising regulations, ethics, and structural guidelines. Ongoing issues concerning ownership, transfer agreements and access to materials, intellectual property, access to samples and data, and the return of results and incidental findings also persist, hindering the establishment of a cohesive framework (Caenazzo & Tozzo, 2020).

ELSI Framework for Biobanks in Italy

The GDPR has significantly impacted the regulation of biobanks for medical and scientific research purposes in Italy. It prompted the Italian legislature to provide a comprehensive and general legal framework for treating genetic data, potentially through developing 'codes of conduct' under Article 40 of the GDPR (Cippitani et al., 2022). These codes would be formulated by associations or bodies representing controllers or processors and approved by the competent supervisory authority. Various codes and principles of research ethics have been developed to clarify how researchers should act toward research subjects in an ethically sound manner.

The legal situation of biobanks in Italy is a complex and evolving field which both national and European legislation has shaped. In Italy, compared with other EU countries and their national legal systems, there is no ad-hoc law on biobanks for research, which leads to uncertainties (Penasa & Tomasi, 2021). There is also no

specific legislation for biobank research activities; instead, the protection of the rights of participants and donors must be derived from different legal sources, particularly that of personal data protection (Penasa & Tomasi, 2021). The National Data Protection Authority plays a central role in establishing the regulatory framework for biobanks in Italy, including issuing authorisations and establishing different conditions and guarantee measures (Penasa & Tomasi, 2021). The Italian legal system adopts a hybrid approach to biobanks and genetic data treatment, which delegates the further development of the regulatory framework to the competent administrative authority.

According to Italian law and the 'Comitato Nazionale per la Biosicurezza e le Biotecnologie', biobanks are defined as '*service units that must be officially recognised by the appropriate healthcare authority in the member states and must guarantee the treatment, distribution, and conservation of biological material according to standards of quality and professionalism*'(Cannovo et al., 2020, p. 3). However, different definitions of 'biobank' have been proposed in the Italian national and international literature (Fedeli et al., Cannovo et al., 2020; 2019). Furthermore, biobanks are not explicitly regulated, and the legal and regulatory frameworks regarding their use are fragmented, with variations across different fields of medical research (Calzolari et al., 2013). Accordingly, Italian law does not offer specific itineraries for achieving this legal status. In consequence, the regions have taken the initiative to complete local legislative itineraries to reorganise the sector

(Cannovo et al., 2020). These activities are governed mainly by guidelines and 'soft law' instruments, such as nonbinding recommendations issued by ethics committees and scientific associations (Calzolari et al., 2013).

Analysing the Italian and EU legislative and regulatory frameworks that govern biobanks reveals the issue of not only the privacy of the subject from whom the data are taken but also the identity, dignity, and freedom of self-determination regarding one's physical integrity due to the detachment of a part from the rest of the body (Vergallo, 2021). The terminology also requires caution, as terms and concepts such as 'anonymised' can be misleading. This is because the biological material of a human being that is not genuinely anonymous is still being used, and it is or might still be possible to identify the person through DNA fingerprinting (Elger & Caplan, 2006). Furthermore, the sample cannot be anonymised without valid informed consent. Otherwise, the donor would be deprived of the right to choose whether to allow their biological material to be used for other research and their right to withdraw consent. Instead, to be complete and consistent with the personalist approach adopted by the Italian Constitution, a person's self-determination must also extend to the use of the separate parts of their body as they share its genetic identity (Montanari Vergallo et al., 2016; Vergallo, 2021).

Other unresolved issues are, for example, that obtaining a minor's consent in collecting minors' biological samples has not yet been lawfully addressed (Cannovo et al., 2020). By contrast, patents and

data protection are governed by binding directives (Calzolari et al., 2013).

The Biobanking and BioMolecular Resources Research Infrastructure – European Research Infrastructure Consortium (BBMRI-ERIC) plays a significant role in elaborating such a code of conduct, aiming to find a balance between research needs and individuals' rights and freedoms in the context of biobanking (GDPR and Biobanking, 2021; "News – A Code of Conduct for Health Research," 2023; Penasa & Tomasi, 2021). According to BBMRI-ERIC, Italy has 82 biobanks. It is imperative to list biobanks with locators to provide transparency, promote accessibility, and prevent duplicated efforts (O'Donoghue et al., 2022).

Background to the CHRIS biobank

The CHRIS study is a longitudinal cohort study based in South Tyrol, Italy, linked to a biobank located in Bolzano and Meran (Pattaro et al., 2015). Further, the CHRIS study cooperates with the South Tyrolean Health Care System (Azienda Sanitaria dell'Alto Adige).

As part of a population study, the state of health of thousands of people is examined over a long period. From 2011 to 2018, 13,393 Middle and Upper Vinschgau/Val Venosta inhabitants participated in the first phase of the CHRIS study (baseline phase). The second (follow-up) phase began in 2019 and will continue for a few years.

Health data and biological samples are collected from all participants.

CHRIS has adopted a participant-centric approach to collect participants' feedback and address considerations of their needs throughout the research process (Mascalzoni et al., 2021; Pattaro et al., 2015).

Legal Framework for CHRIS

The CHRIS study can store biological samples (e.g., blood and urine) and their derivatives (e.g., DNA and cell lines) in automated freezing systems and computers in their biobanks. The samples and data are stored in pseudonymised (coded) form for 30 years, and the personal and clinical data are stored separately. The data are backed up periodically, encrypted, and stored in geographically separate locations.

Noteworthily, a need exists for a legal custodian of the data and samples for the entire study duration, who is responsible for treating the resources with the utmost care and granting access only to authorised staff for the purposes specified in the consent form. The cell lines obtained from the biological samples will be stored in the biobank for 30 years. They can be used for other research projects after Ethics Committee approval is obtained, thus complying with the provisions of the informed consent form. Participants are asked to permit the retention of the collected material for 30 years after the

date of the last consent and to indicate how the data and samples should be handled in the event of their death or incapacity.

All participants of the CHRIS study possess legally recognised rights under the GDPR. Furthermore, the CHRIS study complies with the Italian law on personal data protection (if the relevant provisions differ from European legislation), the Helsinki Declaration (as amended), the 2016 Taipei Declaration (WMA Taipei Declaration on Ethical considerations on health databases and biobanks), the Convention on Human Rights and Biomedicine (Oviedo 1997, as amended), and the Italian research legislation. CHRIS also follows the international CIOMS guidelines, the guidelines of the National Bioethics Committee, and those of the National Committee on Biotechnology, Biosafety and Life Sciences for the collection of biological samples for research purposes ("CHRIS studio sulla salute - Val Venosta Alto Adige - Eurac Research," 2023). Before participating in the research, participants are informed about the goals and perspectives of the study and sign an informed consent form. Figure 2 presents a comprehensive guide illustrating the essential rights participants possess concerning their data within the CHRIS study.

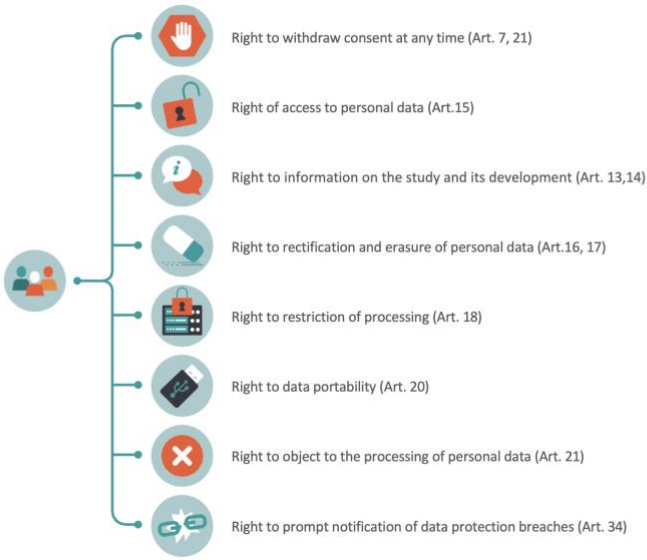


Figure 2: Infographic developed by the Eurac and CHRIS communication team to illustrate the rights of participants under the General Data Protection Regulation (GDPR).

Dynamic informed consent in CHRIS.

The mechanism with which the participants express their decisions in CHRIS is a dynamic, informed consent process (Mascalzoni et al., 2022). This implies that participants receive continuous information as a prerequisite for exercising their right to withdraw from the study or to oppose data processing that they consider inappropriate at any time. The personal platform MyCHRIS ("CHRIS studio sulla salute - Val Venosta Alto Adige - Eurac Research," 2023) contains all relevant, constantly updated information on participation in the CHRIS study and on the use of the data for the various projects in the research areas for which the

participant has given consent. The changes made on this platform are deemed to have been effectively implemented and are, therefore, legally valid.

With this declaration, the participants confirm with a signature that they know all conditions, were informed, and understood their rights before participating in the CHRIS study. They have the right to make and change these decisions, for example, whether they can be recontacted or receive genetic findings and which ones, if available. Further, participants specify whether they want to be informed (right to know), do not want to know the results in any case (right not to know) or only want to be contacted if the results are particularly relevant to their health or the health of their relatives.

Dynamic informed consent and decisions on returning research results to participants.

In the realm of biobank research, one of the critical ethical considerations centres around the return of research results to study participants. To help CHRIS participants decide whether and which results to return, the ELSI group has developed a mechanism embedded in the dynamic consent process that allows CHRIS participants to choose which typologies of hypothetical genetic research results they would like to receive. By providing a detailed description of the typologies, participants are informed and asked a question in the consent form about the particular hypothetical genetic research results that could potentially result from the study. These typologies differ in four elements: Disease risk, prevention

measures, treatment measures and chances of cure. These four typologies are described in detail in the brochure and on the website, and each is illustrated with an example to facilitate the decision based on this information before participating. Videos describing these four typologies in more detail are on the website ("CHRIS studio sulla salute - Val Venosta Alto Adige - Eurac Research," 2023).

The following textbook contains the information on the example of Parkinson's disease (PD):

Parkinson's disease (PD)
Typology 2: Low risk of disease, prevention not possible, treatment possible
Characteristics of the typology: This genetic predisposition leads to a slight increase in the risk of the disease (compared to the general population). Even if the predisposition is known, preventive measures cannot be taken to prevent the disease. However, there are treatment options that can alleviate the symptoms of the disease.
Example: Parkinson's disease is a nervous system disease that leads to the degeneration of nerve cells in certain brain regions. The most common symptoms include tremors, muscle rigidity, slowed movements and, in many cases, balance problems. The first clinical signs typically appear around the age of 60. The disease is multifactorial, i.e. it is triggered by an unfavourable combination of several genetic and environmental factors. There are currently no preventive measures that can prevent the onset of Parkinson's disease, nor can the progression of the disease be stopped. Parkinson's disease cannot be cured, but there are treatment options that can significantly alleviate the symptoms. The risk of developing Parkinson's due to the genetic predisposition described above is very low. It is only slightly higher than the risk of people who do not carry this gene variant. First-degree relatives (parents, siblings and children) also have only a slightly increased risk of developing the disease compared to the rest of the population. In most cases, only one person in the family is affected.

Overarching Rationale of the RbG in CHRIS and ProtectMove

The DFG (Deutsche Forschungsgemeinschaft) funded research unit ProtectMove ("ProtectMove," 2023), involving researchers from the Institute of Neurogenetics at the University of Lübeck and the

Institute of Biomedicine at Eurac Research, investigates the intricate relationship between genotypes and phenotypes in PD.

The study focuses on genotype-phenotype interaction mechanisms, encompassing the concept of 'reduced penetrance', specifically emphasising variants in genes such as Parkin (PRKN). The term 'penetrance' refers to the conditional probability of contracting disease X given a specific genotype and measures the percentage of individuals in a particular population with a specific disease-associated genotype who actually exhibit the corresponding disease phenotype (Cooper et al., 2013; Shawky, 2014). While penetrance relates to the proportion of a population expressing the phenotype, if a given genetic variant is present, 'expressivity' describes the extent to which the phenotype is expressed. The complexity associated with genotype-based therapies can be attributed to reduced penetrance and differences in clinical expression (Bruggemann & Klein, 2019).

As one of the most prevalent and fast-growing neurodegenerative disorders, PD can be caused and lead to various clinical presentations (Bloem et al., 2021; Castelo Rueda et al., 2021). Common complex disorders involve interactions between multiple genes and environmental factors, making it challenging to identify contributing genetic variants and assess associated risks, but also in Mendelian genetics, there are uncertainties due to factors like penetrance and phenotypic variability (Howard & Iwarsson, 2018). PD's origin is likely multifactorial, arising from a complex interplay of largely unknown elements: multiple genes, modifying effects

from susceptibility alleles, environmental exposures, and gene-environment interactions, including how environmental factors affect gene expression and their direct influence on brain development and aging (Klein & Westenberger, 2012). After nearly 15 years of research on it, about 28 chromosomal regions potentially linked to PD have been identified, but only six of these regions contain genes with mutations definitively causing monogenic PD, a form where a mutation in a single gene is enough to trigger the condition (Klein & Westenberger, 2012). The genetic classification of PD involves 18 specific chromosomal regions but has some inconsistencies and includes both confirmed and nonconfirmed loci, some of which do not have identified causative genes or mutations (Klein & Westenberger, 2012).

Through whole genome sequencing, numerous carriers of presumably pathogenic mutations have been identified who show no signs of the disease. Many people carry such variants, and their symptoms are very mild or have certain factors that protect them from possible disease. In autosomal dominant inherited disorders, for example, it is possible for a carrier of a variant classified as pathogenic not to get sick or to show very mild symptoms.

In diseases such as PD, where two mutations are usually required (autosomal recessive), there is evidence that a mutation in a heterozygous state increases the risk for specific clinical symptoms. This is the case for PRKN gene variants that cause genetic PD when two mutations are present (homozygous or compound heterozygous).

However, studying the correlation between genotype and phenotype in these heterozygous individuals is of great interest in the ProtectMove project for comparison with patients with homozygous or compound heterozygous variants. It is uncertain whether and how individual heterozygous mutations in PRKN contribute to the progression of the disease (Camargos et al., 2009). Further studies with carriers of a single gene variant in PRKN compared with patients with two copies are essential to identify possible protective mechanisms that could one day help patients with a disease caused by mutations in this gene.

The CHRIS and ProtectMove study used RbG approaches to investigate the underlying biological mechanisms that contribute to or affect the development of PD and identify potential therapeutic intervention targets. The frequency of heterozygous PRKN variant carriers was investigated in the population sample of the CHRIS study (Castelo Rueda et al., 2021). To follow up on these results, the second funding period intends to identify PD penetrance-modifying factors. To do so, a database with the genomic and lifestyle data collected enables phenotyping and investigating prodromal signs in-depth. The examinations for the RbG2 follow-up study included different tests such as the standardised neurological examination as the MDS-Unified Parkinson's Disease Rating Scale ("MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)," 2023), quantitative motion analysis, transcranial ultrasound, and evaluation by an experienced neurologist form the basis for the interpretation of genetic data. Figure 3 illustrates the examination program and

specific clinical examinations part of the RbG 2 study. Further, in the Appendix, we attached the complete Information material for participants.

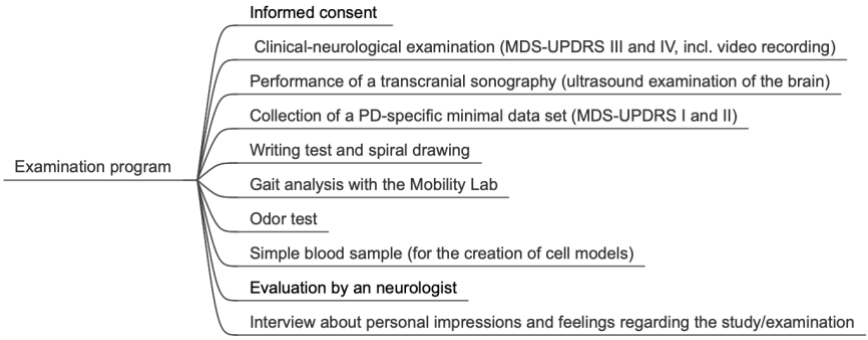


Figure 3: Overview of examination program's specific clinical examinations part of the RbG study.

Feasibility assessment of RbG in the CHRIS study

Researchers evaluated the informed consent procedures used during the study's baseline recruitment to assess the feasibility of conducting an RbG study within the CHRIS cohort. Although there was no specific information on performing RbG studies, the CHRIS study used a dynamic consent model that allowed participants to choose whether they wanted to be re-contacted for further studies and whether they wished to receive information on secondary findings. The researchers selected participants who agreed with both options to identify potential candidates for the RbG pilot study. To ensure participant safety and privacy, the researchers discussed

additional requirements with the CHRIS ethics board and local practitioners. These requirements included confining the study to genetic variants that do not cause pathology with high penetrance and providing a means of direct contact for participants to ask questions about the study.

Test case: Pilot RbG Study (RbG1).

To design the pilot, a feasibility assessment was done, a suitable test case within the ProtectMove Research Unit was selected, and various Teams of the Institute for Biomedicine developed recall and communication strategies in collaboration. The pilot study included an empirical study to understand participants' views on the RbG study (R. Biasiotto et al., 2023). Based on a literature review and consultations with relevant stakeholders (CHRIS participants, clinical geneticists, ethics board, and general practitioners), we identified critical ethical issues in RbG approaches (e.g. complexity of the context, communication of genetic results, measures to further protect participants) and for this specific case and context (Mascalzoni et al., 2021).

In the RbG1 study in 2018, a subgroup of the CHRIS Cohort (27 heterozygous carriers of the PRKN gene variant that may act as a risk factor for PD and 24 matched nonvariant carriers as controls) was re-invited according to the developed RbG ELSI-protocols. CHRIS participants were recalled based on the presence of a particular genotypic variant in the PRKN gene, either genotypically

inconspicuous or with a single heterozygous variant that may slightly increase the risk for some attenuated clinical symptoms.

Disclosure & Communication strategy for CHRIS RbG study

As a critical aspect of the communication strategy, participants were informed about the results they could expect to receive from the study. The information on the individual carrier status was not disclosed, but the disease and the variant studied were. The provided information emphasised the research-oriented nature of the study and that the results would not be disclosed to participants because the results are not suited for genetic counselling, and the implications of the carrier status are unclear.

Laws and policy approaches for the Return of research results.

There are legal implications related to the use and return of genetic information in research processes. Still, often, legal regulations only cover some specific cases, resulting in an incomplete or patchy regulatory landscape. This landscape often adopted or brought contradictory rules forward for researchers, specifically in cases where research collaborations include different countries or even continents (Thorogood et al., 2019; Vears et al., 2021). The legal and ethical guidelines regarding the return of individual genetic research results set different criteria for researchers to decide what

information to return. However, researchers have considerable flexibility in choosing which cases, when and how to communicate the results (Bollinger et al., 2012). Despite the current legislation and research participants supporting the return of research results, practices within biobanks vary, reflecting ambivalence (Goisauf, 2019). Accordingly, researchers may face ELSI challenges when deciding whether and how to return research results to participants. This includes determining which results should be disclosed, how to communicate the findings, and managing potential conflicts of interest (Blumling et al., 2021). Legal, financial, and organisational challenges and the absence of coherent international guidelines and legal frameworks discouraged genetic studies from sharing individual research results with participants (Kösters et al., 2019).

Scholars have demanded clarity in the ethical and policy approach to return results (Thorogood et al., 2019; Vears et al., 2021). The ethical framework needs clarification based on the preferences and perspectives of those most impacted by the policy development for result disclosure (Vears et al., 2021). Further proposed solutions include clarifying legal requirements, aligning practices across Europe and utilising cost-efficient online tools and platforms, while further investigation is needed to assess how institutional challenges, including limited resources, might affect the process of returning research results (Bredenoord et al., 2011; Goisauf, 2019). However, there are lingering questions about who exactly constitutes those most affected by policy development for result

disclosure — whether it is the researchers, the participants, or other stakeholders.

Legal framework for Disclosure and Return of research results in Italy.

In Italy, the legal grounds for the Return of Research Results (RoRR) and disclosure in genetic research in biobanks are governed by a combination of EU law, national law, orders made by authorities, and soft law, which need to be integrated with ethical principles, technological strategies, and solutions (Piciocchi et al., 2018).

The most critical regulations shaping the processing of personal and genetic data for scientific research, as in biobanks, are the General Authorisations issued by the Italian Data Protection Authority, Authorisation no. 8/2016 on the processing of genetic data, and Authorisation no. 9/2016 on the processing of personal data for scientific research purposes (Penasa & Tomasi, 2021). The General Authorisation No. 8/2012 for the Processing of Genetic Data, 2014, authorises the disclosure of individual results by the following:

> *'Genetic test/screening results and/or research findings that entail factual, direct benefits in terms of treatment, prevention and/or awareness of reproductive choices also to the individuals belonging to the same genetic line as the data subject may be communicated to such individuals if they so request and the data subject has expressly consented thereto,*

> *or if the results/findings in question are indispensable to prevent those individuals´ health from being jeopardised – including reproductive risks – and the data subject´s consent is not or cannot be given because the data subject is nowhere to be found.* ("General Authorisation No. 8/2014 for the Processing of Genetic Data," 2023)‘.

Nonetheless, there are unexplored matters concerning the characterisation of a significant genetic disease, and adopting a particular definition may be challenging or not favourable (Battistuzzi et al., 2012; Wertz & Knoppers, 2002). Yet, there is an urgency for established thresholds to clarify the rules on when the disclosure of genetic information to at-risk family members (without the patient’s consent) can be done (Battistuzzi et al., 2012). Understanding how genetic data could affect at-risk family members without the primary patient's direct consent is a crucial ethical and legal consideration in genomic research. The absence of defined criteria poses challenges for researchers, clinicians, and other stakeholders as policymakers alike in navigating the ethical and legal landscape surrounding the disclosure of genetic information to at-risk family members. This lack of clarity emphasises the necessity for ongoing interdisciplinary discussions and collaborations to formulate comprehensive and ethically sound guidelines that balance the patient's rights with the potential benefits to at-risk relatives.

This imperative underscores the need for ongoing discussions and interdisciplinary collaborations to navigate genetic research's complex ethical and legal landscape regarding the disclosure and return of research results.

Aim

In recent years, as RbG studies have become increasingly popular, an urgent need has arisen for a suitable ELSI framework that addresses their peculiarities (Mascalzoni et al., 2021). Moreover, a need also exists for a broader application of the RbG research approach (Budin-Ljosne et al., 2013).

This PhD project aimed to evaluate the ELSI of RbG and assess the CHRIS study's ELSI framework and strategies for disclosing and communicating RbG approaches. The project deliverables included

- an empirical assessment of the RbG studies in CHRIS,
- information material on RbG studies, and
- recommendations for the CHRIS RbG ELSI framework.

We based the assessment of the ELSI framework and adjustment of the RbG policy on primary research that we conducted in the CHRIS RbG context. The findings are discussed along with arguments drawn from ethical, legal, or other normative principles, as in similar research studies (Minion et al., 2018).

To capture the complexity of the context while ensuring the practicality of our recommendations and their alignment with national laws and global bioethical norms, we investigated the ELSI of RbG through both macro and micro-scale considerations.

At a macro scale, it was essential to explore how RbG approaches are applied, the types of scientific rationales in which RbG approaches are employed, and the ELSI that stem from them. By contrast, micro-scale assessments were crucial for collecting the

perspectives and feedback of relevant stakeholders within the RbG CHRIS setting and those regarding the specific scientific rationale of the CHRIS RbG studies investigating genetic variants linked to PD. For the micro-scale assessment, we used insights from 'Ethno-Immersion in (Empirical) Bioethics' by (Parsons et al., 2023), and the ELSI research focus on proximity to assess micro-scale ELSI and challenges through empirical research with relevant stakeholders.

To this end, we explored ELSI aspects through various empirical studies that have assessed stakeholder perspectives and developed RbG information material for participants. Then, we discussed how the findings of empirical work can be translated into disclosure and communication strategies for RbG studies.

The outline below provides a comprehensive overview of the individual studies conducted within this research, along with their corresponding aims, employed methods, and associated chapters.

Overview of specific studies, aims, methods and chapters

Aim	Sub-aim	Method	Chapter
Identify ELSI of RbG & key normative principles	Map the investigative area, assess the existing knowledge, and identify critical issues and tensions in RbG research from an ELSI perspective	Conducting a Scoping review	1
Analysing participant's views on ethical implications of RbG	Collect insights into participant's motivations for participating in RbG studies, responses (emotions, concerns) to invitations, the impact of disclosure on them, identify conditions that might influence participants' willingness to participate	Performing a secondary analysis of a mixed methods study on the results from the Pilot RbG study (RbG1)	2
Analyse participant's views on disclosure and communication strategies of RbG in the CHRIS context	Collect insights into participant's views, expectations and concerns in terms of disclosure and communication strategies	Develop and perform quantitative questionnaire tailored to the CHRIS participants of the PAREGEN 2 study (RbG2)	3
Investigate and analyse stakeholders' views on ELSI of RbG in the CHRIS context	Understand the perspectives of individuals directly involved in the design, practical aspects, and feedback from the direct interaction with participants	Designing and Conducting Focus Group Discussions with relevant stakeholders	3
Analyse participants views on disclosure and communication strategies of RbG in the CHRIS context	Collect insights into the contextual importance of different aspects of the study design and preferences regarding communication and disclosure strategies	Large-scale survey, in the form of a quantitative study, with CHRIS baseline participants	3
Evaluate ELSI in the CHRIS RbG study context Adjust the ELSI framework and RbG policy of the CHRIS study	The analysis will generate draft recommendations for policy design in RbG approaches based on the perspectives of relevant stakeholders derived from the analysis of the empirical investigation results	Discussion on research results through empirical investigations	4

Finally, material developed during this doctoral study, through a collaborative approach involving researchers, communication teams, and other stakeholders as study personnel is attached. We aimed to create clear and accessible information materials that enhance participants' understanding of the RbG study's purpose, procedures, and potential implications as a deliverable of this PhD project.

1st Chapter: Ethical, legal and social/societal implications (ELSI) of recall-by-genotype (RbG) and genotype-driven-research (GDR) approaches: a scoping review

This chapter is adapted from:

Tschigg, K., Consoli, L., Biasiotto, R., & Mascalzoni, D. (2022). Ethical, legal and social/societal implications (ELSI) of recall-by-genotype (RbG) and genotype-driven-research (GDR) approaches: a scoping review.
Eur. J. Hum. Genet., 30, 1000–1010.
doi: 10.1038/s41431-022-01120-y

Abstract

Recall by Genotype (RbG), Genotype-driven-recall (GDR), and Genotype-based-recall (GBR) strategies are increasingly used to conduct genomic or biobanking sub-studies that single out participants as eligible because of their specific individual genotypic information. However, existing regulatory and governance frameworks do not apply to all aspects of genotype-driven research approaches. The recall strategies disclose or withhold personal genotypic information with uncertain clinical utility. Accordingly, this scoping review aims to identify peculiar, explicit and implicit ethical, legal, and societal/social implications (ELSI) of RbG study designs.

We conducted a systematic literature search of three electronic databases from November 2020 to February 2021. We investigated qualitative and quantitative research methods used to report ELSI aspects in RbG research. Congruent with other research findings, we identified a lack of qualitative research investigating the particular ELSI challenges with RbG. We included and analysed the content of 25 publications.

We found a consensus on RbG posing significant ethical issues, dilemmas, barriers, concerns and societal challenges. However, we found that the approaches to disclosure and study-specific recall and communication strategies employed consent models and Return of Research Results (RoRR) policies varied considerably. Furthermore, we identified a high heterogeneity in perspectives of

participants and experts about ELSI of study-specific RbG policies. Therefore, further fine-mapping through qualitative and empirical research is needed to draw conclusions and re-fine ELSI frameworks.

Background

For more than 15 years, Next-Generation Sequencing (NGS), Whole-Genome-Sequencing (WGS) and Genome-Wide-Association- Studies (GWAS) powered the integration of genomic data, enabled personalised medicine approaches, and led to an increase of scientific knowledge translation from biology to the societal dimension (communicating genetic risk to the individual participant) (Kumar, 2020; Loos, 2020; Zeggini et al., 2019). To further analyse the vast amounts of genotypic data, targeted bottom-up approaches to select participants are gaining popularity versus conventional random sampling strategies (Atabaki-Pasdar et al., 2016; Corbin et al., 2018; Franks & Timpson, 2018; Minion et al., 2018). Recall by Genotype (RbG), and Genotype-driven-research (GDR) strategies are bottom-up models to recall participants for genomic research and phenotyping selectively based on the presence or absence of a specific genotypic variant. Genotype-driven selection strategies pose a powerful tool for identifying causalities between genes and diseases, specifically in cases when genotypes are rare, and phenotyping of extensive sampling frames would be too costly (Finer et al., 2020; Franks & Timpson, 2018;

Momozawa & Mizukami, 2021). Furthermore, when studying human subjects with specific genotypes, there is a higher probability of detecting underlying disease mechanisms and genetic associations, even though defining risks for the individuals among the identified variants is not easy (Minion et al., 2018; Momozawa & Mizukami, 2021).

Similarly, defining study policies respective to the recruitment/recall phase, the consent procedures, and the Return of Research Results (RoRR) policies is challenging as RbG approaches have not been outlined fully and are bound to the consent and context of the original or parent study (Corbin et al., 2018; Taylor et al., 2017). The RbG study design relies on dividing participants of an original large scale study into smaller groups; accordingly, a crucial balance between sample size and statistical power must be kept (Zeggini et al., 2019). Moreover, the economic benefit of decreasing sample sizes for RbG is weighed against the particular ELSI considerations that arise, including the risks emerging from classification practices in genomics, biased datasets and a lack of diversity, and the risk of genetic discrimination and stigmatisation (Burke, 2021; Cambon-Thomsen et al., 2007; de Vries, 2019; Hartman et al., 2020; Howard & Iwarsson, 2018; Momozawa & Mizukami, 2021; Zeggini et al., 2019). There is a need to have further discussions on the ethical issues involved in RbG (Mascalzoni et al., 2021).

We conducted a scoping review to identify ethical issues and debates with nuanced ELSI considerations regarding different

frameworks' scientific and societal utility to guide the complexities of RbG study design decisions. Considering that ethics goes beyond complying with current legal and regulatory requirements, we will discuss uncertainty, unaddressed issues, diverging study design considerations and missing recommendations of ELSI of RbG.

Methodology and objective

We used the scoping review methodology (Arksey, 2005) and reported it according to PRISMA guidelines (Tricco et al., 2018). According to PRISMA guidelines, we conducted the search from November 2020 to February 2021.

Identifying the research question

The main objective of this scoping review is to identify peculiar, explicit and implicit ethical, legal, and societal/social implications (ELSI) of RbG study designs and then discuss the following review questions:

1. What are ethical, legal, societal or social (ELSI) aspects of RbG research?
    a. How do different approaches to RbG studies handle the identified ELSI issues in terms of disclosure strategy, study-specific recall and communication strategies, employed consent models and Return of Research Results (RoRR) policies?
2. What type of qualitative and quantitative research and methods

were used to report ELSI aspects in RbG research?

3. What are the ELSI debates, issues and future concerns collected from participants and other stakeholders in RbG research?

To synthesise these review questions, we will discuss consensus, conflicts and diverging recommendations on ELSI of RbG that need further investigation.

Search strategy

As a prerequisite to the scoping review, we identified all the relevant terms for RbG studies through iterative search runs in the different databases, as shown in Figure 4. The databases searched were Web of Science, PubMed (Medical Literature Analysis and Retrieval System Online, MEDLINE), Science Direct, and Google Scholar. The search included all types of documents.

Detailed search strategy (Web of Science) and search terms and strings

Search publications with RbG* in the Abstract (AB) OR Title (TI).

For readability reasons we will use the term RbG as a umbrella term to address all the identified terms illustrated in Figure 1.

AB= (RbG*= recall-by-genotype OR recall-by-genotype-research OR recall-by-genotype-based OR genotype-driven-recall OR genotype-driven-recruitment OR genotype-driven-recontact OR genotype-driven-research OR genotype-driven-research-recruitment OR genotype-guided-recall OR genotype-guided-recruitment OR genotype-guided-research OR genotype-guided-research-recruitment OR genotype-informed-recall OR genotype- informed-recruitment OR genotype-informed-

recontact OR genotype-based-recall OR genotype-based-recontact OR genotype-based-recruitment OR genotype-based-research OR genotype-informed-recruitment OR genotype-informed-recall OR genotype-informed-recontact OR genotype-informed-recall OR recruit-by-genotype OR recontact-by-genotype)

Indexes and filters: Timespan: All years.

RbG * AND AB= (ethic* OR ELSI OR ELSA)

RbG * AND AB= (legal*)

RbG * AND AB= (societal* OR social*)

We replicated the search strategy on Pubmed, Science Direct and Google scholar.

The use of the asterisk (*) wildcard implies that the search is expanded to similar words.

Figure 4: Detailed search strategy, search terms and strings.

Article selection and eligibility criteria

We included documents written in English. We excluded publications with a clinical focus that did not discuss ELSI aspects (for example, publications that did not discuss ELSI aspects beyond the explicit reporting of compliance and procedural ethical approval processes). We included publications with qualitative and quantitative methods and empirical elements. Exclusions were confirmed by using Endnote X9 and Rayyan filters and manual review. We did not apply any time limitations. KT performed the search and screening. The co-authors verified the screening for accuracy. The selection of eligible and relevant literature was

discussed among the authors. Seventy publications were selected for full-text screening and assessed for eligibility. We included 25 publications in the synthesis of the review. Figure 5 demonstrates the detailed selection process and the eligibility criteria formulated to identify relevant publications that address ELSI in RbG.

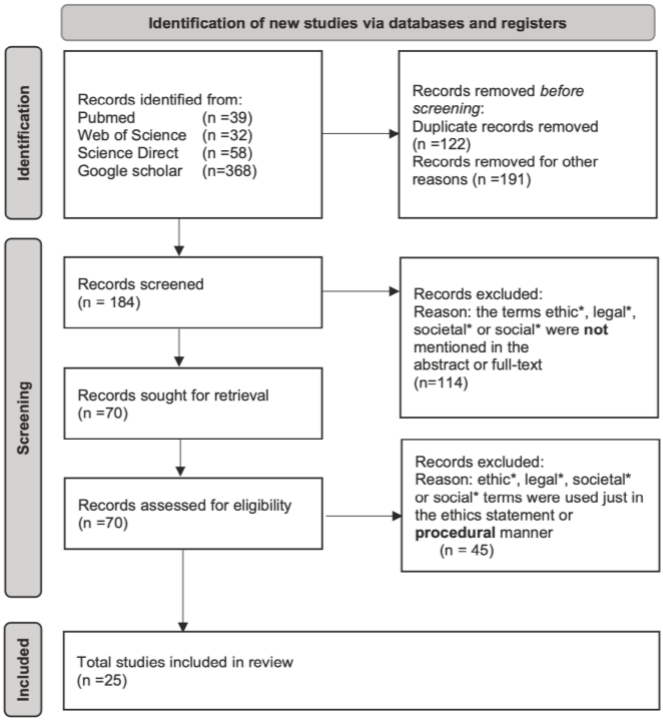
Data extraction, charting and synthesis

Publications were retrieved, organised and managed with Endnote X9 and Rayyan to track eligibility decisions systematically (EndNote X9, 2020; Ouzzani et al., 2016). We charted the eligible selection into Microsoft Excel and Word tables to extract data. KT conducted the content analysis with an inductive approach to analyse the contextual use of the searched terms and compile a matrix of themes and considerations from the publications. The identified themes were discussed among the authors and agreed upon.

Results

Following a full-text review, we included 25 studies in the synthesis (as shown in Appendix) (Atabaki-Pasdar et al., 2016; Beskow, 2017; Beskow et al., 2004; Beskow et al., 2012; Beskow et al., 2010; Beskow et al., 2011; Beskow, 2012; Budin-Ljosne et al., 2013; Cadigan et al., 2011; Corbin et al., 2018; Doernberg & Hull, 2017; Finer et al., 2020; Franks & Timpson, 2018; Khera & Kathiresan, 2017; McGuire & Lupski, 2010; McGuire & McGuire, 2008;

Michie et al., 2012; Minion et al., 2018; Momozawa & Mizukami, 2021; Namey & Beskow, 2011; Oliver et al., 2012; Olson et al., 2014; Ossorio & Mailick, 2017; Tabor et al., 2011; Taylor et al., 2017).



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71

Figure 5: Identification of relevant literature. PRISMA referred flowchart about the process of searching and identifying relevant literature. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71

We identified an overall lack of qualitative research investigating the ELSI of RbG. Out of the 25 included publications, we

discovered nine empirical data collection methods on ELSI of RbG, as shown in Table 2. We ordered this chronologically to demonstrate the evolution of the different studies, some of which were in direct response to another.

There is a consensus from the literature that RbG poses significant ethical and societal challenges with ELSI discussions centred on the themes shown in Table 1. Most publications focused ELSI concerns on the Recruitment phase, couples with the RoRR policies because research results from an original study are the basis for identifying and recalling participants for further investigation with the specific RbG study. Another recurring discussion regarding the ethical duty to disclose results (and which types of results) and the ethical issues and concerns regarding explicit and implicit disclosure of research results as carrier status came up. Further, publications reported ethical barriers and challenges concerning the different suitable consent procedures or the lack thereof. The theme of how to tailor procedures to the context of the specific study was discussed by empirical studies searching for balances and using anticipatory research to adjust the study design and policies to the context.

Table 1: Main themes identified with the content and thematic analysis in the included publications.

Main themes in RbG research	**Themes addressed by the publications**		**Results**
	Description of identified ELSI discussion on	**Specific consideration or recommendation**	
study design, stakeholder engagement, and policy development	ethical balance	between scientific interests and the participant's rights and preferences	(Beskow et al., 2004; Beskow et al., 2012; Beskow et al., 2011; Cadigan et al., 2011; Corbin et al., 2018; Minion et al., 2018; Olson et al., 2014; Ossorio & Mailick, 2017; Tabor et al., 2011; Taylor et al., 2017)
		protecting research participants while avoiding overly restrictive policies	
		balance the potential harms with or without disclosure	
	scientific and statistical considerations	about RbG compared to other recruitment frameworks	(Atabaki-Pasdar et al., 2016)
	ELSI considerations for the study design and how to tailor approaches to the context and cohort	how to translate ELSI considerations into practical RbG policies	(Beskow et al., 2012; Budin-Ljosne et al., 2013)
		practicalities of incorporating genotypic data into population-based study	(Corbin et al., 2018)
		ethical implications of familial research in RbG	(Beskow et al., 2004)
		implications of bottom-up approach	(McGuire & McGuire, 2008)
		practicalities of linking genotype information with electronic health record (EHR)	(Finer et al., 2020; Khera & Kathiresan, 2017; Taylor et al., 2017)
recall frameworks: invitation of participants	explicit and implicit disclosure by invitation: ethical principle of autonomy pitched against the right not to know unwanted genetic information	how to avoid deception and inform participants (about study purpose, eligibility criteria and the return of research results policy)	(Beskow, 2017; Beskow et al., 2012; Beskow et al., 2010; Beskow et al., 2011; Beskow, 2012; Budin-Ljosne et al., 2013; Doernberg & Hull, 2017; Minion et al., 2018; Ossorio & Mailick, 2017; Taylor et al., 2017)
		practicalities of no-disclosure of the targeted genetic variant	(Beskow, 2017; Beskow et al., 2010; Doernberg & Hull, 2017; Ossorio & Mailick, 2017; Taylor et al., 2017)

consent procedures	informed consent (Beskow et al., 2004; Beskow et al., 2012; Beskow et al., 2011; Beskow, 2012; Minion et al., 2018; Namey & Beskow, 2011; Tabor et al., 2011)	harmful or deceptive characteristic if research is conducted in the absence of disclosure and informed consent	(Doernberg & Hull, 2017; Taylor et al., 2017)
		dynamic consent	(Budin-Ljosne et al., 2013)
		'presumed' consent	(Franks & Timpson, 2018)
return of research results policies (RoRR)	how to return unsubstantiated, uncertain, unexpected, incidental or indeterminate findings and research results (Beskow, 2017; Beskow et al., 2012; Beskow et al., 2011; Cadigan et al., 2011; Doernberg & Hull, 2017; McGuire & Lupski, 2010; Michie et al., 2012; Minion et al., 2018; Namey & Beskow, 2011; Olson et al., 2014; Tabor et al., 2011; Taylor et al., 2017)	how to communicate the details of research results (personal and clinical utility)	(Beskow, 2017; Beskow et al., 2012; Beskow et al., 2011; Cadigan et al., 2011; Doernberg & Hull, 2017; McGuire & Lupski, 2010; Michie et al., 2012; Minion et al., 2018; Namey & Beskow, 2011; Olson et al., 2014; Tabor et al., 2011; Taylor et al., 2017)
		'No return of results' policy	
risks and uncertainties	potential distress triggered by the invitation or study participation	disclosure of eligibility criteria can lead to differently derived meaning in patients and participants	(Beskow et al., 2011; Namey & Beskow, 2011) (Michie et al., 2012) (Beskow et al., 2010) (Corbin et al., 2018) (McGuire & Lupski, 2010)
		communication about distinct risks	(Beskow et al., 2004)

		ELSI issues linked to benefits and risks associated with sharing genomic data	(Oliver et al., 2012)
		uncertainty about how genetic information will be used in the future	
		discrimination	
introduce new techniques to society	whether ethics-related recommendations suffice for broader use of RbG approaches		(Budin-Ljosne et al., 2013)
	paediatric RbG		(Tabor et al., 2011)
	development of tools	to promote education, dissemination and public engagement	(Budin-Ljosne et al., 2013)
		less intrusive but faster and more efficient recruitment through electronic tools	
	careful societal considerations about specific populations		(Momozawa & Mizukami, 2021)
	electronic health record and other information are needed for artificial intelligence to integrate genetic and nongenetic information		

RbG research and corresponding methods used to explore ELSI aspects

Since 2002 there has been an increase in the use of RbG sub-nested in various large-scale genomic research settings. However, except for a review on ethical implications of familial genetic research and RbG, before 2008, there is no consideration of the specific ELSI of RbG (Beskow et al., 2004). Most identified publications employing and reporting empirical data collection methods are situated in the UK- or US-based research context.

We identified an overall lack of data on the experiences and opinions of various stakeholders such as participants. The employed

methodologies to collect stakeholders' perspectives on ELSI of RbG were qualitative interviews with participants that were either recalled for genotype-driven research or not eligible for the RbG study but purposively sampled (Beskow et al., 2011; Cadigan et al., 2011; Michie et al., 2012; Minion et al., 2018; Namey & Beskow, 2011; Oliver et al., 2012; Tabor et al., 2011). Other literature on stakeholders and experts like researchers, clinicians, policymakers (Beskow et al., 2011; Cadigan et al., 2011; Minion et al., 2018; Namey & Beskow, 2011; Tabor et al., 2011) may lack diversity in reporting the perspectives of different stakeholders because all the publications are derived from the UK- or US-based research context. There is a minimal body of research discussing the results of mixed-methods approaches with experts such as members of the Institutional Review Board (IRB) in the US and other well-trained researchers or scholars on RbG (Beskow et al., 2012; Beskow et al., 2010; Beskow, 2012). Current ELSI studies about RbG tend to involve stakeholders with a narrow range of characteristics in terms of education and cultural background, as reported in detail in Table 2.

Table 2: List and details of the publications employing qualitative and empirical data collection methods to investigate ELSI of RbG (n=9), (slightly adapted to fit the format: Year column was deleted, Title and ref was merged).

Title of the publications	Method	Recruitment strategy	Sample size	Participation rate	Characteristics of the sample	Country where the study was conducted
Ethical challenges in genotype-driven research recruitment (Beskow et al., 2010)	Commentary and case presentation of a quantitative RbG study	The invitation letter was sent to all study participants (n = 975)		The quantitative study reported a response from 51 (5.3%). Of these: 37 (72.5%) opted out of any further contact about the follow-up study and 12 (23.5%) called to volunteer for the follow-up study. Two (3.9%) withdrew from the parent study		US
Research participants' perspectives on genotype-driven research recruitment (Beskow et al., 2011)	qualitative study, interviews	Purposive sampling strategy where approx. half of the included participants had been recontacted for RbG, and the other half was not.	n=78		As reported, approximately two-thirds were female, and most were white, nonHispanic, and college educated (as a function of the sample in the original study).	US
The meaning of genetic research results: reflections from individuals with and without a known genetic disorder Cadigan et al., 2011)	qualitative research, in-depth interviews	Individuals were selected based on the presence of genetic traits.	n= 24 (Cystic Fibrosis participants n=9; Biobank Participants n=15)		As reported, all participants in the interview study were White and nonHispanic, reflecting the racial and ethnic composition of the study population. Overall, the respondents were well educated, particularly the biobank participants. As reported, several of the biobank participants are themselves scientific researchers or physicians or had previously worked in scientific research positions.	US
Epilepsy patient-participants and genetic research results as 'answers' (Namey & Beskow, 2011)	qualitative research, semi-structured in-depth interviews, part of a multi-site study (Beskow et al., 2011)	Purposive sampling: about one third of epilepsy patient-participants that had been recontacted about the genotype-driven follow-up study	n=29	Of 26 epilepsy patient-participants eligible for the genotype-driven follow-up study, nine completed and interview and of 24 patient-participants who were not eligible 20 completed an interview	As reported, most of our interviewees were female, white, nonHispanic, and college educated.	US
Parent perspectives on paediatric genetic research and implications for genotype-driven research recruitment (Tabor et al., 2011)	qualitative research, interviews with parents of epilepsy patient-participants	6 of the parents experienced RbG recruitment and 17 did not	n=23		As reported, most of the participants were mothers, Caucasian, and had at least a bachelor's degree.	US
IRB chairs' perspectives on genotype-driven research recruitment (Beskow, 2012)	Qualitative research, Survey with commercial and institutional IRBs	Targeted institutional and commercial IRBs in the US	n=201	50% completed the survey	As reported, most of the participants were white, nonHispanic males, age 50 or older. The most IRBs reported more than 4 years of service as an IRB chair and had a professional background in medicine or social science. As reported, over 80% chose 'academic institution' as the best descriptor of their current institution and 17% IRBs reported to have been involved in reviewing a protocol involving genotype-driven recruitment.	US (online survey)
Recommendations for ethical approaches to genotype-driven	Workshop, Multisite study, with multiple	wide range of stakeholders - discussion was informed by	n=34 affirmed their agreement		stakeholders in RbG research: researchers, study coordinators, and participants from studies,	US

Title of the publications	Method	Recruitment strategy	Sample size	Participation rate	Characteristics of the sample	Country where the study was conducted
research recruitment (Beskow et al., 2012)	stakeholders, including some study participants - in-depth interviews with research participants	empirical data of (Beskow, 2012) - in-depth interviews with research participants in six studies where genotype-driven recontact occurred (Beskow et al., 2011; Cadigan et al., 2011; Namey & Beskow, 2011; Tabor et al., 2011)	on the final recommendations		as well as bioethics scholars, IRB leaders, other genomic and biobank researchers, clinicians, and federal officials engaged in issues related to human subjects research	
Am I a control?: Genotype-driven research recruitment and self-understandings of study participant (Michie et al., 2012)	Qualitative research, same interviewees as for (Cadigan et al., 2011)	eligibility criteria included the presence of one of two genetic variants. (Cystic Fibrosis participants n=9; Biobank 'healthy volunteers' Participants n=15)	n= 24		As reported, all 24 interviewees were self-reported as White and nonHispanic (reflecting the racial and ethnic composition of the study population). The respondents were generally well educated, particularly the biobank participants.	US
The ethics conundrum in Recall by Genotype (RbG) research: Perspectives from birth cohort participant (Minion et al., 2018)	qualitative research, semi-structured interviews	The purposive sampling strategy sampled participants across three categories: (1) general ALSPAC cohort participants who had never participated in an RbG study; (2) participants who had participated in an ALSPAC RbG study; and (3) individuals who had served on one or more ALSPAC committees at which RbG study applications were discussed	n=53	final response rate (26.5%) (200 ALSPAC participants received an invitation email and 74 expressed interest)	As reported, the participants are young adult participants of the Avon Longitudinal Study of Parents and Children (ALSPAC). As reported, of the 53 participants interviewed, 29 were female, and 51 has been enrolled in ALSPAC continuously since birth.	UK

Data with and without context

We identified significant differences between RbG studies accompanied by qualitative or empirical research and those without an empirical element. Furthermore, we found that empirical research on ELSI of RbG derives from US- or UK-based studies. We identified differences in how publications reported and contextualised participation rates of quantitative RbG studies and response rates for qualitative and empirical studies, as shown in Table 2. These differences need further attention. Some of the

differences stem from and relate to the specifics of the respective RbG research study and its population and are therefore to be discussed in the context.

ELSI aspects in different RbG study designs and policies

The targeted genotype-driven research approach tests a hypothesis. Accordingly, the researchers can better anticipate and communicate the potential research results for prospective or recalled participants than in untargeted WGS and GWAS (Beskow, 2017; Beskow et al., 2004; Beskow et al., 2010; Corbin et al., 2018). In line with other research, we identified a lack of consensus and standardised approaches, methods and boundaries to classify and communicate the clinical validity and utility of the individual carrier status from the original study (WGS or GWAS) (Beskow et al., 2010; Franks & Timpson, 2018). However, participants might not be informed about why they are eligible if the genetic results, which are the reason for eligibility, are not disclosed (Olson et al., 2014). This, in turn, might invalidate the participant's informed consent for the respective study. We identified a lack of a best practice on the decision to explicitly or implicitly obtain re-consent for RbG follow-up or substudies. We found no consensus on best practice on whether it is necessary to disclose the carrier status with uncertain clinical utility/validity. Likewise, we identified substantial differences in strategies to explain the study objective (in-depth or more general)

and distinct reactions of participants and patients to the different disclosure strategies. (Beskow et al., 2010; Franks & Timpson, 2018).

We identified review studies foreseeing 'ethical barriers' and concerns linked to the use of 'presumed' consent where the explicit consent from older cohorts (or potentially dead participants) is not given due to cost and time (Franks & Timpson, 2018). In such studies, a waiver of consent from an ethical Review board enabled the RbG or another strategy where study policies were adjusted to an opt-out model (Franks & Timpson, 2018; Olson et al., 2014). For example, an Icelandic genomics company successfully reasoned that explicit informed consent was unnecessary because of public support and security measures (Franks & Timpson, 2018).

Publications on family-based recruitment in RbG reported that consent requirements should be left to the investigators and the IRB (Beskow et al., 2004). Some US-based IRBs preferred not to offer individual results due to statements from the original consent and potential negative consequences. For example, in a study investigating gene variants associated with epilepsy, the disclosure of unsubstantiated findings confused some of the participants' (Beskow et al., 2010). Studies demonstrated a high level of heterogeneity in IRB members' views. However, most IRBs prioritised avoiding disclosure of genetic information with uncertain clinical utility rather than prioritising participant autonomy to make judgements and draw conclusions about the usefulness of the data (Beskow, 2012). There is a lack of standard practice on several key

aspects: deciding whether it is necessary to explicitly or implicitly disclose the carrier status and design a suitable communication strategy in alignment.

ELSI debates about disclosure by invitation and the 'is there something wrong with me'? question

There have been recommendations to reduce distress for participants in the recall phase by involving the same elements as 'trusted researchers' or the same institution as the original study and highlighting that an invitation to the specific RbG does not imply a particular genotype or phenotype (Beskow et al., 2011; McGuire & McGuire, 2008). However, this explanation of the study design and eligibility criterion for the respective RbG study can evoke different reactions depending on the respective disclosure and communication strategy employed and the person's individual experience. We identified substantial differences between the different groups as participants and patients. The reactions to the study invitation range from concerns as 'Why? Did you find something wrong with me? (Beskow et al., 2010)' to 'am I a control (Michie et al., 2012)' assumptions about the individual's group membership to perceptions on RbG study as 'just another study' (Minion et al., 2018).

The heterogeneity of reactions stems, among other factors, from the fact that the participants feel different motivations depending on

whether they are part of the 'healthy' population group as controls or patients with a manifested genetic disease. Some individuals are carriers of a genetic variation that may or may not be disease-causing. Others are carriers of a genetic trait that does not (yet) have a corresponding phenotype. Whereas patients may experience no or low levels of concerns, healthy participants may assume or derive meaning when being invited to an RbG study (Beskow et al., 2011; Cadigan et al., 2011; Corbin et al., 2018; McGuire & Lupski, 2010; Michie et al., 2012; Namey & Beskow, 2011; Tabor et al., 2011). There are significant differences in how the two groups conceptualised genetic research results as meaningful and accordingly also the preferences for receiving the results diversified (Cadigan et al., 2011). However, the relevance of validity and/or utility linked to research results appeared in interviews with healthy participants and patients (Cadigan et al., 2011). Some participants of these interviews carried an underlying 'bad news' assumption in which results are implied to offer negative but definite information about a genetic condition, although the information material and invitation to the study stated otherwise (Cadigan et al., 2011). These different reactions lead to concerns about the potential distress, uncertainties or anxieties triggered by the recall and disclosure strategy in the scientific community (Beskow et al., 2010; Beskow et al., 2011; McGuire & Lupski, 2010; Michie et al., 2012).

Caution is needed to avoid cascade effects triggered by the assumed meaning because potentially harmful or unnecessary efforts to confirm findings with uncertain significance have been highlighted

(McGuire & Lupski, 2010). To avoid some of the mentioned distressed reactions to the recall process, a few studies decided not to disclose the targeted genetic variant and use more general language when describing the study objective (Beskow, 2017; Beskow et al., 2010; Doernberg & Hull, 2017; Ossorio & Mailick, 2017; Taylor et al., 2017). In another strategy of an empirical study with RbG, participants reported about the use of a nondisclosure policy that was developed with a community board and accepted by participants because of: trust, a limited literacy on genetics and modest interest in research outcomes, and the perceived role in research participation as 'data providers (Minion et al., 2018)'.

Qualitative data from interviews revealed that participants exhibit a high degree of heterogeneity in deciding whether to obtain research results with uncertain validity, but a consensus regarding the researcher's 'duty to tell' why they want to study their specific genetic sample (Namey & Beskow, 2011). The desire to know might negatively affect participation rates if participants are not provided with an explanation for why they are eligible for a specific RbG. It could perpetuate uncertainties and assumptions on clinical or personal utility or the reasons of eligibility for the RbG study. In cases where the investigated genetic variant is linked to a stigmatising condition, the decision to conceal or disclose the genetic variant 'cannot be made without the input of participants themselves' (Minion et al., 2018). We suggest further empirical research about participant engagement and involvement in study

governance decisions to fine-map the considerations necessary for different study designs and informed consent procedures.

ELSI debates and the quest for balance

We identified limited empirical studies, and they were predominantly based in the UK and US. We identified differences in how the invitation process happens and linked recommendations, from no disclosure - (Beskow, 2017; Beskow et al., 2010; Doernberg & Hull, 2017; Ossorio & Mailick, 2017; Taylor et al., 2017) to implicit disclosure (Beskow et al., 2012; Doernberg & Hull, 2017; Ossorio & Mailick, 2017) to explicit disclosure of the study objective or genetic variant targeted. Similarly, we identified differences in what kind of consent and RoRR policy was employed and discussed (Beskow et al., 2004; Beskow et al., 2012; Beskow et al., 2011; Beskow, 2012; Budin-Ljosne et al., 2013; Doernberg & Hull, 2017; Franks & Timpson, 2018; Minion et al., 2018; Namey & Beskow, 2011; Oliver et al., 2012; Tabor et al., 2011; Taylor et al., 2017); from broad and lifelong to detailed, informed electronic and dynamic; as shown in Table 1 and 2.

Many publications addressed the importance of balance and the implications on designs and policies for RbG, from balancing the scientific interests and the participant rights and preferences to balancing the protection of research participants while avoiding overly restrictive policies and the balance between the potential harms with or without disclosure. Some of these ELSI risks might

be partially minimised by adding a sub-group of randomly or voluntarily selected participants to the specific RbG study sample group (Beskow, 2017; Beskow et al., 2011). Other publications reported on identified ELSI risks and harms of RbG in terms of a lack of representativeness and inclusivity. These risks associated with diversity and utility require more ELSI considerations and research and performative dimensions that tackle the lack of diversity and translational benefit and health disparities in genomics in general (Burke, 2021; Hindorff et al., 2018).

Discussion

Considering the urgency for shared ethical and legal frameworks to use the abundance of available genomic, geno- and phenotypic data, understanding and mapping the ELSI uncertainties is crucial to the evolution of RbG (Borry et al., 2018; Momozawa & Mizukami, 2021). ELSI challenges in RbG were thoroughly analysed in 2013 and raised the concern that this study design is not yet outlined with concise recommendations to use the approach in a broader spectrum of research (Budin-Ljosne et al., 2013). However, are we at the point yet, where we have outlined and refined the study design appropriately to use it in a broader spectrum of research?

When designing invitation and disclosure strategies, there is no easy, one-size-fits-all solution to decide about whether, how and when to disclose the individual carrier status during the invitation

process or not (Beskow et al., 2010; Kaufman et al., 2008; McGuire & Lupski, 2010).

The analysis of the empirical studies confirmed the lack of qualitative data from diverse stakeholders and contexts. Accordingly, more diversified empirical studies about the context and outside the US/UK are needed. This research is crucial to understanding the differences in patients' and healthy participants' reactions to RbG study invitations.

Ethical and social/societal challenges need more empirical research to contextualise quantitative data as the participation and response rates with qualitative data in different RbG settings. Furthermore, this contextualisation of participation and response rates might help determine weak spots or a lack of understanding in the communication trajectory surrounding the respective RbG study. Measures to check the understanding of participants in RbG would therefore be valuable.

Similarly, the ELSI of disclosure of the individual carrier status with uncertain clinical utility might need more clarification in the communication trajectory with participants.

Acknowledging the contextual aspects of RbG through empirical, qualitative and normative research will refine the frameworks for RbG in the quest to find balances.

RbG studies cannot be seen as isolated; the context and the consent of the original study shape the study design for the sub-study significantly. To find balance and to tailor the study policies to the context, the specific cases should be informed by anticipatory

research on the specific RbG study and the context to the parental or original study. Providing tailored approaches that can cope with the identified heterogeneity of preferences and expectations of stakeholders requires tracing 'unruly ethics' with qualitative research (Felt, 2008). These empirical insights will provide a better understanding of the possibilities and limitations of upstream engagement of participants and patients to re-fine ELSI frameworks. Some of the identified ELSI issues in RbG are termed as 'ethical conundrums' because they are novel challenges needing balances to respect the principle of autonomy adequately and not compromise the 'right not to know' (Minion et al., 2018). Many ethical dilemmas of RbG, which can be framed as unruly or conundrums, are not yet addressed extensively enough to formulate a best practice and to have a consensus on the ethical approval of a recruitment or disclosure strategy. Further qualitative research is needed to redefine appropriate approaches for different RbG studies and contexts to overcome the difficulty of informing participants thoroughly about the particular RbG study without creating anxiety. This is especially true for RbG studies where the genetic variant can be a stigmatising factor, or the re-invitation is unexpected (Mascalzoni et al., 2021; Minion et al., 2018).

Nevertheless, we identified a broad agreement that participants want to understand why they are eligible (McGuire & Lupski, 2010; Michie et al., 2012; Minion et al., 2018). Given that actionability and personal utility are drivers of participation, more research is needed on expectations in RbG and respective RoRR policies and

linked communication to participants. The development and advancement of efficient electronic communication tools that decrease the time for recruitment and consent procedures require further attention to avoid overburdening participants and families, violating public trust or implicit social contracts and affecting the willingness to participate negatively (Budin-Ljosne et al., 2013; Budin-Ljosne et al., 2017; McGuire & McGuire, 2008).

However, obtaining viable sampling frames for specific RbG research studies will remain a practical, financial and logistic challenge. Utilising other population data may be a strategy to obtain statistical power, quality-control and produce robust science (to avoid mismatches as in the example of a Greenland-and Japan-based study of associations between variants in Type 2 Diabetes (Atabaki-Pasdar et al., 2016; Momozawa & Mizukami, 2021). Nevertheless, there are legal and ethical challenges with big data and cross-border sharing for global research approaches because legal compliance alone does not address the safeguarding function necessary for the complexity of data-driven research (Borry et al., 2018; Svantesson & Bentzen, 2017; Vayena & Blasimme, 2018). RbG studies require further ELSI considerations to safeguard research participants, collectively and individually, from potential unexpected discrimination to provide more than the legal and ethical minimum through technical measures such as pseudonymisation (Borry et al., 2018). In research settings in low-income countries, the increasing involvement of commercial interests and industries, paired with weak governance structures and the unlikely immediate

translational benefit from the commercialisation of genomics, may decrease trust and the willingness to participate in genomic research (de Vries, 2019; Singer & Daar, 2001). Further societal considerations on how to increase diversity and inclusivity for GWAS, WGS and RbG sub-studies are needed to tackle the unequal access to translational benefits from and in genomic research and precision medicine (Burke, 2021; Gurdasani et al., 2019; Wojcik et al., 2019).

We identified clear points of contention between researchers and research ethics review committees. These stem from utilising substantial distinct ethical frameworks that guide decisions regarding socioeconomic and practical factors (Ballantyne, 2019; Ballantyne et al., 2020). Some researchers discouraged the sharing of RbG research results with uncertain validity because of, among other things, not enough time and economic resources to implement processes to prevent these issues (McGuire & Lupski, 2010; Purvis et al., 2020). We identified various prioritising schemes in defining the necessity to obtain re-consent for various RbG studies. This was due to the acknowledgement of different threats from the more comprehensive data-sharing environment to justify not obtaining consent, as in the cases of the ‘care.data scheme (Sterckx et al., 2016)‘ and the ‘Icelandic case (Franks & Timpson, 2018)‘. Presumed accordance with changes towards an opt-out consent model and life-long static consents and institutional and legal solutions that enable the re-use of data for RbG might run into the risk of violating trust because of being the ethical minimum (Franks

& Timpson, 2018; Sterckx et al., 2016). The focus on institutionalised bioethics and individual consent for data-driven research settings are insufficient to address ethical and social/societal challenges (Ballantyne, 2019; Beskow et al., 2010; Kaufman et al., 2008; Mascalzoni et al., 2021).

Other RbG pilot studies included concise premises as eligibility requirements in the original consent procedure about the recall, communication and return of genetic findings to allow recalling participants of the original study for further RbG with an ethically sound strategy (Mascalzoni et al., 2021). Approaches, with a dynamic consent and specified choices in terms of recall (for which studies) and if and how research results (with un or certain clinical utility) can enter the real-time of the individual, may address some ELSI concerns of RbG. By this, participants' can adapt the given consent to their changing perspectives and needs, which is not given in the case of a life-long consent. Even if dynamic consent may be a partial solution to some shortcomings in consent procedures, more empirical cases are needed to determine how to provide the highest utility of dynamic consent models (Pacynv et al., 2020).

However, these apparent differences in strategies to conduct RbG studies lead to concerns about scientists' self-governance. Research practices should be transformed by ethics and not be limited to adapting the consent models and using ethics as a ritualistic language to 'smooth over moments of dislocation' and the political dimensions of practices (Am, 2019). Because of endemic problems such as the differences in knowledge, epistemological biases and

pressing financial and time issues, making ‘the ELSI perspective heard (Conley et al., 2020)‘ does not suffice to have a real-time ELSI influence on policies in genomics.

In conclusion, this review led to an overview of ELSI in RbG and shed light on understudied issues that require further qualitative research. The findings herein serve to map and generate an understanding of the different stakeholder’s perspectives on the ELSI strategies used in RbG studies that need to be investigated further. We identified areas with compelling or contrasting qualitative research results that require further attention and clarification to re-fine ELSI frameworks for RbG. As such, these findings contribute to the further development of qualitative studies linked to RbG follow-up or sub-studies in large research and biobanking repositories.

Authors' contribution

As a prerequisite to the scoping review, KT and the ELSI Team identified all the relevant terms for RbG studies through iterative search runs. The terms were discussed among the authors to ensure comprehensiveness. Additional searches were based on expert suggestions.

KT performed the screening process, selected the publications for full-text screening, assessed their eligibility, and executed the screening and exclusion process. The selection of eligible and relevant literature was discussed among the authors. KT retrieved, organised, and managed publications. KT performed the data extraction and charting. KT conducted the content analysis, and the results were discussed between the authors. KT drafted the first manuscript and designed all the figures.

2nd chapter - Participant perspective on the recall-by-genotype research approach: a mixed-method embedded study with participants of the CHRIS study

This chapter is adapted from:

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Abstract

Recall-by-genotype (RbG) research recruits participants previously involved in genetic research based on their genotype. RbG enables the further study of a particular variant of interest, but in recalling participants, it risks disclosing potentially unwanted or distressing genetic information. Any RbG strategy must therefore be done in a manner that addresses the potential ethical and social issues. As part of an RbG pilot on the penetrance of Parkinson's disease variants, we conducted an empirical mixed-method study with 51 participants of the Cooperative Health Research in South Tyrol (CHRIS) study to understand participant views on RbG research approach. Participants were disclosed the disease under investigation but not the individual variant carrier status. Results showed that participants filtered the information received through personal experience and enacted mechanisms to address the concerns raised by invitation by resorting to personal resources and the support provided by experts. While the nondisclosure of the Parkin variant carrier status was deemed acceptable, disclosing the disease under study was important for participants. Participant preferences for disclosure of the disease under investigation and the carrier status varied according to how the knowledge of individual carrier status was perceived to impact the participant's life. This study provided insights into participant response to the RbG research approach, which are relevant for RbG policy development. A suitable communication strategy and granular options addressing

preferences for invitation in the original informed consent are critical for an ethically informed RbG policy.

Introduction

A recall-by-genotype (RbG) research approach consists of inviting individuals who previously participated in genetic research based on their specific genotypes. The aim is to efficiently study the phenotype of those carrying specific variants of interest (Corbin et al., 2018).

This research approach, which is becoming increasingly popular thanks to the large availability of genotyping data from the most recent sequencing technologies, poses legal and ethical challenges. Inviting participants and providing information on the research study may imply disclosing genetic information, disease risk, and unwanted or distressing information (Beskow, 2017; Beskow et al., 2012; Beskow et al., 2010; Doernberg & Hull, 2017; Taylor et al., 2017). For this reason, exploring participant perspectives on the RbG approach is crucial to improve research practices and develop suitable policy. The Cooperative Health Research in South Tyrol (CHRIS) study, a longitudinal study with the general population of Val Venosta/Vinschgau, South Tyrol in Italy, conducted its first RbG study in a sub-sample of the CHRIS cohort (pilot RbG study) as a joint project with the University of Lübeck, in the framework of the ProtectMove Research Unit project (FOR2488), in 2018 (Mascalzoni et al., 2021; Prasuhn et al., 2021). The ProtectMove

project investigates movement disorders, including Parkinson's disease. The pilot RbG study aimed to investigate the phenotypic features of carriers of heterozygous Parkin variants. The variants under study, carried in a heterozygous state, had low penetrance, leading to mild or no neurological symptoms.

Our study, a mixed-method empirical study embedded within the pilot RbG study, aims to understand participant perspectives on RbG research approach and participant experience of invitation and participation in a specific RbG study. The present work was motivated by process of policy design for RbG studies within the CHRIS study (Mascalzoni et al., 2021). A participant-centred approach, which considers participant views, is key in the CHRIS study, which uses dynamic consent as an informed consent model (Biasiotto et al., 2021; Mascalzoni et al., 2022; Pattaro et al., 2015).

Methods

Study setting

The CHRIS study focuses on age-related neurological, cardiovascular, and metabolic health and diseases and their genetic, environmental, and lifestyle determinants (Pattaro et al., 2015). The study, which started in 2011, collects data and biological samples from a closed cohort of 13,389 adult participants enrolled between 2011 and 2018. The mother tongue of most residents in Val

Venosta/Vinschgau is German (Mascalzoni et al., 2022). Participant recruitment and the broader empirical RbG study have been described elsewhere (Mascalzoni et al., 2021; Prasuhn et al., 2021) and summarised in Table 3.

Table 3: Pilot RbG study and recruitment of participants. A total of 58 participants were invited to the pilot RbG study, with the strategy de-scribed in the table.

Project	The ProtectMove Research Unit project, focused on Parkinson's disease and other neurological movement disorders, aims to investigate the genetic penetrance of specific variants of many genes, including the Parkin gene.
Pilot	In order to guarantee participants' safety, the RbG was conceived as a pilot study focused on heterozygous Parkin variants that are pathogenic when inherited recessively in a homozygous or compound heterozygous state, but may influence symptoms dominantly, with very low penetrance, in a heterozygous state. Carriers of heterozygous Parkin variants may show subtle signs of PD, slight abnormalities in the dopaminergic system (Hilker et al., 2001; Khan et al., 2002), morphometric changes in the basal ganglia (Binkofski et al., 2007), and compensatory changes in functional MRI studies (Anders et al., 2012). The pilot study consisted of deeper neurological examinations, transcranial ultrasounds, and quantitative movements assessment to explore the genotype-phenotype relationships in heterozygous carriers versus noncarriers.
Design	The study was designed with a matched recruitment, where half of the invited participants carry the Parkin variant of interest in a heterozygous state, and the other half, who do not carry the variant, serve as controls. Controls were chosen as closely related to the carriers, with similar age and same sex, if possible.
Invitation	Participants were invited through the mail, which included a letter and information on the study.

Information provided in the invitation	The invitation explained the aim of the study, disclosed the disease and the variants under study, and the study's design. Participants were informed that, according to current knowledge, heterozygosity of the Parkin variant under study does not cause Parkinson's disease, but may cause an increase of the risk of prodromal neurological symptoms. As being a carrier of the variant in a heterozygotic state is not associated with any known clinical benefit, participants were informed that individual carrier status would not be disclosed.
Disclosure	Both researchers and participants did not know the participant's individual carrier status (double blind).
Further communication	Invited participants were provided a phone number to call to ask clarifications and questions, if needed, and received a phone call from the study assistants to fix an appointment for the clinical examination and the empirical study.

Mixed method rationale

The research was designed with a mixed-method approach with a convergent design (Creswell & Clark, 2017; Tariq & Woodman, 2013).

Quantitative and qualitative methods were used as a complementary strategy.

Data analysis and results interpretation were conducted as follows:

1) Quantitative and qualitative data were collected through two questionnaires and a semi-structured interview. The questionnaire and the interview guide were similar in their general structure and

content to offer participants both written and verbal tools to express opinions and share emotions (Supplementary Information 1).

2) Quantitative and qualitative data were first analysed separately with suitable methods.

3) This was followed by an integrated interpretation of the results: The quantitative results were interpreted and incorporated ad hoc within the themes found with the thematic analysis.

Data collection

Data collection occurred in Schlanders/Silandro (Italy) at the CHRIS study centre on August 20-24, 2018. The workflow was as follows:

1. First questionnaire;
2. Clinical examination conducted by medical doctors;
3. Interview;
4. Second questionnaire.

DM and MK jointly conducted the interviews in German and collected fieldnotes. The approximate duration of the interview was 20 min. Due to time constraints in the daily workflow, respondents sometimes answered the second questionnaire before the interview. In four cases, the second questionnaire was filled in together with the interviewers, which helped respondents go through the questions.

Data analysis

Quantitative data

Descriptive statistics of the quantitative data was generated using Microsoft Excel.

Qualitative data

The interviews were recorded and transcribed verbatim by a professional transcription service. The German transcripts were translated into the English language using Deepl Pro Advanced. Transcripts were analysed using thematic analysis according to the six-step process described by Braun and Clarke (Braun & Clarke, 2006). Our approach was grounded in critical realism/contextualism, i.e., reality is interpreted through participant experiences within broader social context (Stainton Rogers & Willig, 2017; Ussher, 2002). Coding and theme development were with an inductive approach. First, RB became familiar with the interview content by repeatedly reading the transcripts and annotating memos. Second, with an iterative approach and an ongoing coding development and refinement process, the author categorised the data by developing initial codes. Fieldnotes collected by the authors who conducted the interviews and memos generated during the data familiarisation were helpful in this process. Third, the codes were grouped through an abstraction process to generate broader concepts. Candidate themes and sub-

themes, and their relationship as well, were developed. In steps 4 and 5, themes were reviewed, then defined and finalised. Lastly, findings were reported in an analytic narrative. Exemplary quotes were included ad hoc to support the interpretation (in Results). The exemplary quotes are indicated with an 'I' followed by a number to identify each individual interview. Findings were situated within the existing relevant literature (in Discussion).
ATLAS.ti 8 and Microsoft Excel were used as data management and analysis software.

Validation of translation

To validate the translation, KT, a German mother tongue, verified the correspondence of the English translation with the original texts in German. As a further step, MK, a German mother tongue, and KT independently coded part of the German transcripts using ATLAS.ti 8. RB compared, assessed and confirmed the overall consistency of the coding in English and German.

Results

A total of 50 CHRIS participants invited to participate in the study agreed to participate (100% of the RbG study participants). A relative of one of the invitees asked to join and was included in the empirical study. One participant left the study centre without participating in the interview. As a whole, 51 participants responded

to the questionnaires, and 50 participated in the interview. Table 4 shows the socio-demographic characteristics.

Table 4: Socio-demographic description of participants. Participants included 24 females and 27 males. Participants' age was in the range of 25-80 years. Female respondents' median age was 48 years, and the age range was 31-80 years. For male respondents, the median age was 47 years, and the age range was 25-75 years.

Age range (years)	N
25-34	12
35-44	8
45-54	12
55-64	13
65-74	2
>75	4
Education	
Primary school	1
Lower secondary school	5
Vocational school	22
Upper secondary school	13
University or higher	10
Total	51

We identified four main themes. They represent patterns of meaning concerning participant response to RbG invitation and participation. Participant response was thematised as follows:

a) **Information filter through personal experience**:

Participants filtered received information through personal experience. This occurred through reflecting on heredity and the reaction to receiving the invitation.

b) **Stress relief mechanisms**:

Participants enacted mechanisms to alleviate stress related to the invitation and participation in an RbG study. They consisted in resorting to personal resources and in seeking support from experts.

c) **Targeted information matters**:

Targeted information was important for participation. Participants decided based on the information received, and participant engagement depended on the information received.

d) **Expectations on disclosure**:

The expectation concept included what is desirable (or nondesirable) and acceptable (or nonacceptable) to know or not to know in an RbG study scenario. Participant preferences for disclosure of the disease under study and of the carrier status varied according to how the knowledge of individual carrier status was perceived to impact participant's life (Table 5).

Table 5: How the knowledge of individual carrier status is perceived to impact a participant's life determines preferences for disclosure. The scheme of participant preferences for disclosure of individual carrier status according to the type of variant (causing a disease, not causing a disease).

		How knowledge of the individual carrier status is perceived to impact participant's life		
Type of variant	Variant that does not cause a disease	Knowledge allows awareness		Knowledge is - Irrelevant - Unnecessary burden
	Variant that causes a disease	Knowledge allows - Possible action (prevention and/or treatment) - Coping	Knowledge allows action (prevention and/or treatment)	Knowledge is a burden
Participant preference for disclosure of carrier status		↓ Disclosure	↓ Conditional disclosure	↓ No disclosure

Information filter through personal experience

The qualitative data analysis showed that, while reasoning on their recruitment and interpreting the invitation, participants resorted to their own experience and concept of genetic disease transmission. They inferred risk and carrier status from the disease's familial history and other family members' invitations. For example, inviting more people from the same family made a few participants

presume that the whole family was a carrier of the genetic variant or was affected by the disease:

> *When I got the invitation, my mother got the invitation at the same time, and my two half-siblings didn't. That made me think a bit at first, because I thought, okay, it could also be that I got this gene from my mother and from my biological father and, as my two siblings have a different father, didn't get the gene, because they probably don't carry it or don't carry it in duplicate. That was my first train of thought. Then my mother's sister and her son were also invited. So, I thought, maybe it's something that really affects the whole family, because four people from one family is quite a lot. I47*

The invitation made participants think about Parkinson's disease and the risk of developing the disease. They reflected on their health, speculated on their carrier status, and the possibility of genetic transmission of the variant to future generations. In the questionnaire, more than half of the participants thought about the possibility of being carriers of the Parkin gene variant (Table 6, A1).

Table 6: Results of the survey. For easy comparison with the original questions of the questionnaires (Supplementary Information 1), question number (Qn) and questionnaire number (qn) are also reported.

Answer n. (An) (Qn, qn)	Topic of the question	Results			Interpreted within the theme
A1 (Q2, q2)	After the invitation, thought about being a carrier of the variant associated with Parkinson's disease	Yes	27	52.9	Information filter through personal experience
		No	21	41.2	
		Not answered	3	5.9	
A2 (Q3, q2)	Concern about being carrier of the Parkin gene variant	Very concerned	1	2	
		Concerned to some extent	11	21.6	
		A little concerned	17	33.3	
		Not at all concerned	17	33.3	
		I don't know	3	5.9	
		Not answered	2	3.9	
A3 (Q7, q2)	Perceived likelihood of not carrying the variant	Very likely	9	17.7	
		Rather likely	3	5.9	
		Neither likely nor unlikely	19	37.3	
		Rather unlikely	14	27.5	
		Very unlikely	5	9.8	
		Not answered	1	2	
A4 (Q5a, q2)	Comparative risk perception of developing Parkinson's disease following invitation (risk perception higher today compared to risk perception before receiving the invitation)	Do not agree	20	39.2	
		Rather not agree	6	11.8	
		Neither agree nor disagree	17	33.3	
		Rather agree	5	9.8	
		Agree	2	3.9	
		Not answered	1	2	
A5 (Q5b, q2)	Comparative assessment of feeling worried about developing Parkinson's disease following invitation: feeling more worried today compared to before receiving the invitation	Do not agree	21	41.2	
		Rather not agree	6	11.8	
		Neither agree nor disagree	15	29.4	
		Rather agree	7	13.7	
		Agree	0	0	
		Not answered	2	3.9	
A6 (Q4, q2)	Self-assessment of the risk of developing Parkinson's disease	Very high risk	1	2	
		Increased risk	5	9.8	
		Low risk	18	35.3	
		No risk	5	9.8	
		I don't know	21	41.2	
		Not answered	1	2	
A7 (Q8, q2)	Familial history of Parkinson's disease	Yes	18	35.3	
		No	31	60.8	
		Not answered	2	2.9	

Answer n. (An) (Qn, qn)	Topic of the question	Results			Interpreted within the theme
A8 (Q1, q1)	Satisfaction with information received before participation	No, many questions were not answered	2	3.9	
		No, some questions are still unclear	3	5.9	
		Yes, most of the questions were clarified	22	43.1	
		Yes, all the questions were answered	20	39.2	
		Not answered	4	7.8	
A9 (Q10, q2)	Satisfaction with information received at the study centre	No, many questions were not answered	0	0	
		No, some questions are still unclear	0	0	
		Yes, most of the questions were clarified	14	27.5	Stress relief mechanisms
		Yes, all the questions were answered	36	70.6	
		Not answered	1	2	
A10 (Q11, q2)	Clarification of questions and doubts during participation	Yes	49	96.1	
		No	1	2	
		Not answered	1	2	
A11 (Q13b, q2)	Disclosure of the disease under study	Yes	45	88.2	
		No	3	5.9	Targeted information matters
		This is not important to me	0	0	
		Not answered	3	5.9	
A12 (Q9, q2)	No return of genetic research results	That's fine with me	42	82.4	
		I think that's a pity	8	15.7	
		I don't care	0	0	
		Not answered	1	2	
A13 (Q6, q2)	Willingness to know the individual carrier status relative to Parkin	Yes	27	52.9	
		No	23	45.1	
		Not answered	1	2	
A14 (Q13a, q2)	Evaluation of the practice of not disclosing the disease	Very negative	8	15.7	Expectations on disclosure
		Rather negative	17	33.3	
		Partly negative/partly positive	16	31.4	
		Rather positive	8	15.7	
		Very positive	1	2	
		Not answered	1	2	
A15 (Q13c, q2)	Impact of the type of disease in willingness to know the disease under study	Yes	27	52.9	
		No	23	45.1	
		Not answered	1	2	

Participants expressed different degrees of concern related to being a carrier of the variant and of the perceived likelihood of belonging to the control group (A2, A3). Participation in the RbG study caused an increase in worries and risk perception of developing

Parkinson's disease only in a small fraction of participants (A4, A5). Additionally, data showed that participants struggled with estimating the risk of developing the disease (A6: 41% chose I don't know). 35% of participants reported a family history of Parkinson's disease (A7).

Stress relief mechanisms

In the interviews, a few participants observed that the invitation raised concerns and often temporary worries. These were solved by resorting to personal resources and the experts' support. Personal resources consisted in re-reading the letter several times and consulting family members. Support from experts consisted of face-to-face conversations with the medical doctors conducting the clinical examination and interactions with the study assistants, medical doctors, and researchers involved in the study. Participation at the study centre was perceived as a positive and comfortable experience. Consulting the experts provided relief, reassurance, and an opportunity for further clarification:

> *I had to read the form twice, because the first moment I saw it, my first thought was: do I have Parkinson's disease or something? […] Then, you don't read through very carefully […] you read it with fear and maybe you only read out what you are already afraid of. And then I gave it to my husband to read and he read it more thoroughly and then I read it again myself*

> *and then I really understood that it was actually, as the doctor explained it to me today. And the doctor's explanation again today made it clear to me what it's all about. […] it was very helpful to get rid of fear and also to know something about how this research works and proceeds. I16*

A trend in emotions before and after participation was found through the quantitative data analysis. By comparing the distribution of the scores assigned in the questionnaire to each emotion at the time of the invitation and after participating in the study, the number of participants reporting positive emotions (carefree, delighted, relieved) with high intensity increased after participation, while the number of participants reporting negative emotions (nervous, anxious, worried) with high intensity decreased after participation (Figure 6).

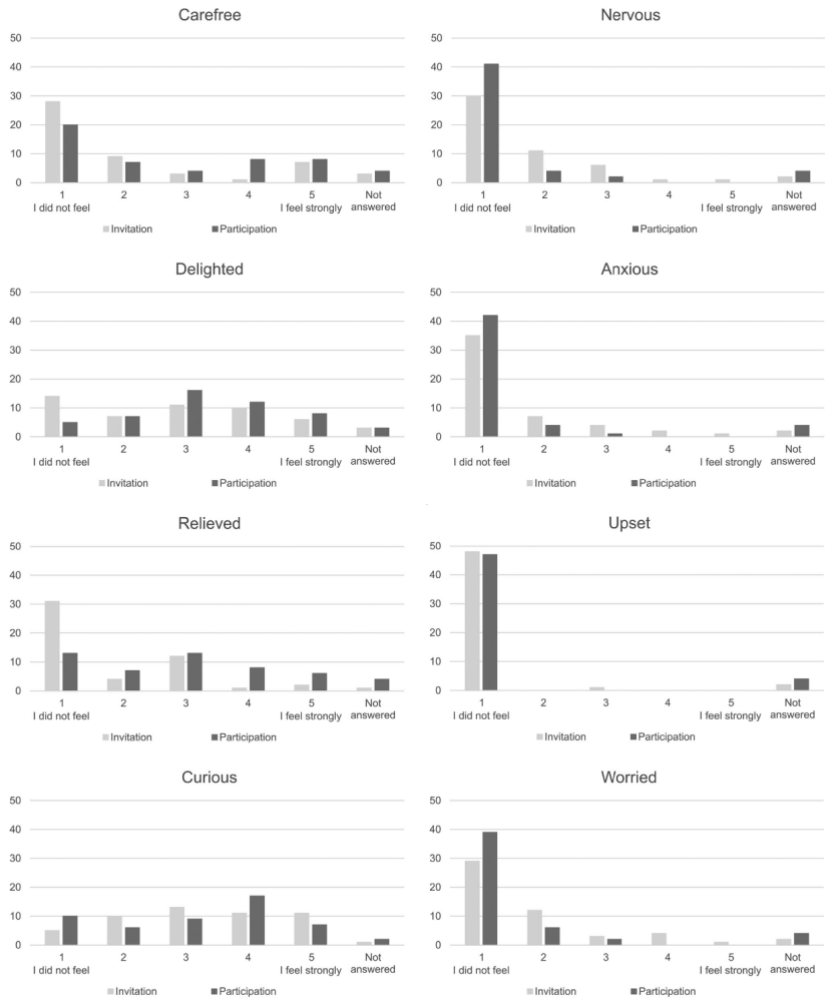


Figure 6: Participants' emotions. Emotions at the time of receiving the invitation and after participation are shown in light gray and dark gray, respectively. On the y-axis, the number of participants reporting the indicated score (1 to 5) is shown.

For the 'curious' emotion, a specific pattern on the score assigned was not identified. Participants reported not feeling upset when receiving the invitation or after participating (except one). Additionally, none of the respondents regretted being invited to the study (50 did not prefer not to be invited, and one not answered).

A similar positively correlated trend was found in the satisfaction with the information received before and after the visit: before coming to the study centre, only a minority of the participants had questions unanswered or unclear; after participation, almost all respondents found that most or all their questions were addressed and answered, and had their doubts adequately clarified and addressed (Table 4, A8, A9, A10). In the interviews, participants raised issues of clarity, complexity, exhaustivity, and amount of the material provided as elements that affected their understanding of the information received in the invitation.

Targeted information matters.

Qualitative data showed that participants saw participation in the Parkin RbG study as a contribution to a meaningful cause with benefits for future generations and society. Personal interest in the clinical examinations and utility for own health were also reasons, shared by most participants, for participation:

> *I can help research with it [through participation in the study, Ed], but it also helps me, because I really do get a health check-up for free. I23*

> *I found it interesting that something is being researched. Because I want to contribute to the results and if you can help, then why not. […] I thought that this could also be of use to me. If something turns out or if there are interesting things in the future. I15*

Additionally, motivations for participation were contextualised in terms of engagement with the CHRIS study:

If you get an invitation, then it is somehow an obligation to go. I46

Quantitative data showed that most participants would like to know the disease associated with the gene variant under study (Table 6, A11). The analysis of qualitative data showed that, while nondisclosing the disease under study would negatively affect the willingness to participate and engagement, the interest for the specific disease under investigation worked as a motivator for participation:

> *I am a nurse and have therefore often had to deal with Parkinson's patients in my life. My grandmother had Parkinson's disease. And a very good friend of mine had a very early form of Parkinson's when she was just over 40. And I personally would be happy to support any study on this subject, like many other studies, if I could. I35*

A few participants clarified that being informed on the area of investigation and the aim of the study was important, not only to be aware of what they were contributing to but also not to feel objectified and instrumentalised as research participants:

> *From my point of view, it is important to inform participants, considering that they participate as volunteers, otherwise, someone will be treated as a guinea pig or something. Blood is taken and one doesn't know where and for what, and I would be in favour of the information simply being available. I14*

On the other hand, for a few respondents, the decision on participation was not based on the disease under study and disease disclosure.

Expectations on disclosure.

The survey showed that most participants were fine with genetic research results not being returned to them in either individual or aggregated form (Table 6, A12). Correspondingly, interview respondents deemed the practice of no return of genetic research results (either individual or aggregated results) acceptable. Participants expressed the view that genetic research results had no direct value for them and that they served for research purposes only:

> *I am not interested in the findings for research purposes […] I am not a researcher. I49.*

Participants distinguished genetic research results from clinically relevant or actionable findings, which were expected to be returned, given their possible utility for their and their family's health:

> *For me it is simply important that if I am really a risk patient, and that is clear from the results, that there is something coming up for me, and above all for my family, that I am perhaps informed. So, basically about genetic information, I can't do anything with that. I13.*

Genetic research results were perceived to affect family also in a negative way:

> *I think if I knew that I had some kind of genetic change that would lead to some kind of serious illness or something, then I would maybe decide not to have any more children […] Then I would be afraid. So, it would really be a drastic life change if you knew that. Then I would probably spend ages finding out whether I should have another child or not, or it would make me feel insecure. I18*

The quantitative data showed that respondents were split into two approximately equal groups as regards willingness to know their individual carrier status with respect to the Parkin variant under investigation (Table 6, A13). However, during the interviews, the majority of participants deemed the nondisclosure of the Parkin gene carrier status acceptable. Given that heterozygosity does not lead to the development of Parkinson's disease, disclosing the carrier status was considered irrelevant, useless, and without diagnostic or predictive value for a few participants. A few participants not only found the nondisclosure acceptable but also

did not want to know their carrier status because they perceived that such information would cause unnecessary burdens and concerns (e.g., being aware of one's heterozygous condition may affect family planning). On the other hand, a few participants would have liked their carrier status to be disclosed: In this case, their motivation was curiosity or/and they found that such information contributed to their awareness about their health:

> *I think I would worry, I don't know, but I think I would listen to myself more purposefully or pay more attention to changes. […] I don't think I would be more afraid, but I think that on the one hand I would pay more attention and perhaps go to a doctor earlier, which could also be helpful. I23*

Quantitative data showed that almost all participants were willing to participate in further RbG studies (94.12% yes, 1.96% no, 3.92% not answered). Almost half of the participants evaluated not disclosing the disease under study in RbG studies negatively. In contrast, 17,65% in a positive way, and 31,37% found it partly positive and partly negative (Table 6, A14). For more than half of the participants, the type of disease would impact their decision about being willing to know the disease under study (A15). During the interviews, participants were challenged with a hypothetical scenario in which an RbG study on a variant that increases the risk for a serious disease was conducted. They were explained that in such a case, they would have their carrier status disclosed and were asked to state their preference for being

recontacted or not for participation and to explain their views. When provided scenarios, a variety of preferences were returned. Participants who wanted to know their carrier status saw its disclosure as a positive opportunity for prevention and actionability. This information was also seen to provide an awareness of susceptibility, which is essential for the development of responses and coping processes:

> *I would like to know, you can prepare yourself somehow. You also have to protect the family somehow, so I would like to know. I13*
>
> *If you have cancer or something, and there is perhaps the possibility that you can treat it at an early stage, it might be better to know at an early stage or what alternatives there might be. […] you can then deal with it a little or talk to people who are in the same situation and exchange ideas, on how are you doing in general, what are you limited in or what keeps you busy or do you somehow need more time for yourself, if you have to somehow cope with your fate now?. I29*

Actionability was used as a criterion for disclosure by those participants who wanted to be invited and to know their carrier status only if opportunities for prevention or therapy were available or in studies about noncausative variants:

> *If there is a therapy, […] then I would like to know. If it's something that you can't do anything about at the*

> *moment anyway, then I personally would rather not know. I28*

A minority of participants did not want to know their individual carrier status nor wanted to be invited to participate in further studies on a pathogenic variant. They perceived that knowing the carrier status of a pathogenic variant was a burden:

> *No, I don't want to know. […] Because then it's always in the back of my mind. I think that with every decision and with everything you have that in the back of your mind. I32*

Table 6 summarises the above-described preferences.

Discussion

The invitation is the first contact in the recruitment process of an RbG study. We found that the information in the invitation was interpreted within a framework of existing knowledge and assumptions of genetic risk and sometimes raised concerns amongst potential participants. Resorting to own resources to understand the role in research and the eligibility for RbG was also acknowledged in another study with biobank participants and cystic fibrosis patients (Michie et al., 2012). After participation in the RbG study, the negative emotions tended to be primarily dissipated, and participants generally felt more at ease. This can be understood within the relief effect provided by the conversation with the medical doctors. These findings showed that information and

support could impact emotions connected to RbG research approaches.

From this study, we observed that:

1) The emotional response that this kind of study may trigger should be considered, and communication strategies that minimise potential distress should be developed.

2) Considering that respondents reported that the amount of material might be a limit, there is the risk that long and detailed letters may be just skimmed instead of being read thoroughly. Therefore, an apt balance between complexity and clarity and between detailed information and an acceptable amount of material should be found.

3) Targeted, transparent and effective communication should be tailored to the variant under study.

Possible practical strategies are:

1) Provide layered information with increasing length and depth.

2) Provide visual tools that allow an adequate understanding of the contents, such as infographics, schemes, and boxes with key concepts.

3) Provide a short glossary with terms that are likely difficult to understand.

4) Identify appropriate lay language to explain research designs, the concept of carrier status, and the risk associated with carrying the variants under study.

5) Provide a contact reference to guarantee the possibility of asking questions and clarifications.

Furthermore, tailoring the communication to the variant under study means that, under certain conditions, it may be necessary to involve medical professionals and genetic consultants from the very first contact. Therefore, it is important to reflect not only on the content and amount of the information provided but also on the timing of different types of communication: which types of communication (written or oral) should come first, in which situations, and how and who should deliver information.

In this study, we found that information affected decision-making on participation and engagement. The disclosure of the disease under study was perceived as part of the transparency-based reciprocity relation between the participant and researcher. As motivators for participation, contribution to the common good and interest in individual health benefits emerged. Also, the value attributed to genetic research results was filtered through the concept of utility: clinically valid or actionable results, valuable because useful vs. research results, irrelevant. These findings align with previous literature, which showed that reciprocity, solidarity, altruism, and utility were important elements in the participant-study relationship and the meaning attributed to genetic research results and disclosure (Cadigan et al., 2011; Michie et al., 2012; Minion et al., 2018; Tabor et al., 2011).

A previous study with CHRIS participants on return of secondary findings showed that participants wished to make autonomous choices about communication and disclosure according to a series of criteria that were important for them to make such a decision

(Kösters et al., 2019). Based on this, the return of result policy of the CHRIS study was refined. With the new policy, participants are provided a model of four sample diseases caused by genetic variants, which differ in risk and opportunity for prevention and treatment ("CHRIS studio sulla salute - Val Venosta Alto Adige - Eurac Research," 2023). In the informed consent, participants are asked to express their preferences for recontacting for each type of genetic variant shown in the model. These choices can be changed over time. Hence, a dynamic informed consent model proved crucial for adequately responding to participant needs and addressing the heterogeneity of participant preferences for disclosure.

In this study, respondents expressed different views on what was acceptable or desirable for disclosure when invited to participate in an RbG study. This depended on the perceived impact that such knowledge would have in their life (burden, awareness, possibility of prevention and treatment). This resulted in different preferences for disclosure and invitation in different situations. Previous literature reported on the importance of clinical validity and clinical utility in affecting biobank participants' and patient cohorts' preferences for disclosure (Beskow et al., 2011; Cadigan et al., 2011).

Based on our findings, policy on RbG approach may be improved by addressing the following points:

1. Participants should be made aware of the possibility of conducting this type of study beforehand.

2. Participants should be offered granular options for consent to participation in RbG studies, and the options should reflect participant preferences.

Empirical studies with different methodologies will allow an in-depth understanding of participant preferences and views, which will allow for further improve the informed consent and RbG policy. The identified heterogeneity of participant preferences has broader research and practice implications. First, researchers should be attentive to what is important for participants and adequately address participant needs and views as partners. Second, as already highlighted in other empirical studies (Beskow et al., 2011; Beskow, 2012; Cadigan et al., 2011; Namey & Beskow, 2011; Tabor et al., 2011), the context in RbG is essential, both in a sense previously identified (Mascalzoni et al., 2021) and at a societal level. Considering the specific disease under study and the meanings attached to it (e.g., possible stigma or discrimination) and the socio-economic conditions (including the access to health care) where the study is conducted would allow a deepened reflection on the societal implications of RbG studies and the extent to which specific research practices are transferrable to other contexts. This implies a limitation in the applicability of the present study's findings in different contexts.

Th embedded design allowed us to elicit perspectives grounded in the experience of participating in an RbG study. The mixed-method research approach was relevant to the research aims. With the analytical strategy that informed the interpretation of the data, the

qualitative results complemented the limitations of the survey results by showing a range of nuances beyond clear-cut numbers and allowing us to understand aspects where the quantitative part became less informative. Given the sample size, our work does not aim to be representative of the CHRIS cohort.

As the analysis was conducted on an English translation, we established measures to ensure accuracy, such as proofreading the translation and comparing independent coding of the German original data and the English version. The results were also thoroughly discussed with one of the authors who conducted the interviews, thus further assessing their adherence to the collected data, meaning, and interpretation.

Conclusion

This study allowed us to identify crucial aspects of participant perspective and response to the RbG research approach. In line with existing recommendations (Beskow et al., 2012; Beskow et al., 2011; Beskow, 2012; Cadigan et al., 2011; Mascalzoni et al., 2021; Minion et al., 2018), this study highlighted the importance of a suitable communication strategy and adequate original informed consent to address the specificities of the RbG research approach. Co-design processes will be crucial for identifying solutions.

The communication strategy and the informed consent model chosen by a research study are key for aptly responding to

approaches that are increasingly widely used in genomics and genetics research, such as RbG approaches.

Data availability

The datasets generated and analyzed during the current study are available in the CHRIS study repository. For an application for CHRIS data, contact the CHRIS study access committee (access.request.biomedicine@eurac.edu). Further information on the CHRIS study is available at https://www.eurac.edu/en/institutes-centers/institute-for-biomedicine and https://it.chris.eurac.edu/.

Authors' contribution

The conception of the study was done by DM, RB. KT translated and validated the translation of the German transcripts, and the coding was compared and confirmed for consistency. KT verified the correspondence of the English translation with the original texts in German. KT contributed to data management and data analysis. Furthermore, KT also revised the manuscript and helped in the review process.

Chapter 3 – Communication and Disclosure in Recall-by-Genotype Research: A Multi-Step Empirical Study in the Context of the CHRIS Study

Abstract

Recall-by-genotype (RbG) is a bottom-up approach using existing genetic data to conduct follow-up studies. Genetic information may be partially disclosed when participants are invited to RbG studies, thus raising ethical issues which call for defined best practices for disclosure and communication in RbG approaches. We investigated research participant and stakeholder perspectives on RbG communication within the context of the Cooperative Health Research in South Tyrol (CHRIS) study and the ProtectMove project, which used RbG approaches.

Methods: This multistage empirical study comprised:

1. A survey with a subsample of CHRIS participants who participated in an RbG study (on heterozygous PRKN variants and Parkinson's disease) to investigate participant views on the specific RbG study.
2. A focus group discussion (FGD) with CHRIS study personnel to investigate the challenges of RbG studies from an operational viewpoint.
3. FGD with researchers experienced in RbG studies to investigate the challenges in study design.
4. A cross-sectional online survey was submitted to a sample of the CHRIS cohort to investigate participant views on possible strategies for RbG disclosure policies and communication.

Results: In step 1, participants (N=96) were satisfied with the PRKN- and PD-focused RbG study process (invitation, rationale, information, informed consent). Most wanted to know their carrier status for personal (coping mechanism or hereditary reasons) and collective benefit.

Tailored disclosure strategies and transparent, effective, and considered communication approaches were advocated by researchers (step 2, N=7) and study personnel (step 3, N=6). Challenges in dealing with uncertainty, concerns caused by RbG invitations, and the possibility of misunderstanding were also raised. In step 4 (N=392), participants valued being informed and generally felt comfortable towards RbG study invitations and receiving genetic information after the RbG study. Comfort and perceived impact of disclosure of genetic information varied according to the type of variant being potentially disclosed.

Conclusion: This study contributes to understanding ethical, social, and practical aspects concerning disclosure, communication strategies, and study policies for RbG. Participants' preferences for disclosure and considerations on relevance and impact should be used to refine the criteria for disclosure and the tailoring of communication.

Keywords: Recall-by-genotype (RbG), disclosure of genetic information, communication, ELSI, empirical research, CHRIS study, research participants, preferences, policy, stakeholder engagement.

Background

The availability of genetic, genomic, and other types of health data in biobanks has rapidly increased translational research while causing interest to proliferate in the ethical, legal, and social/societal implications (ELSI) of these research systems (Bledsoe et al., 2012; Boyer et al., 2012; Cadigan et al., 2013). While the traditional approach to human genetics research relied on a phenotype-first approach, recent discoveries have been made using a 'genotype-first' approach (Mefford, 2009; Wilczewski et al., 2023). In recent years, this advancement has led to targeted bottom-up approaches to participant selection, such as recall-by-genotype (RbG). The RbG or genotype-driven research (GDR) recruitment design (i.e., recruitment based on defined genetic characteristics of interest) has proven to be a powerful tool compared with traditional random sampling strategies. This is particularly so in cases where specific genetic characteristics are rare, and the phenotyping of large sample frames would be too costly (Atabaki-Pasdar et al., 2016; Corbin et al., 2018; Finer et al., 2020; Franks & Timpson, 2018; Minion et al., 2018; Momozawa & Mizukami, 2021). RbG studies reuse biobank material and data, thus decreasing possible public concerns about the underutilisation of biobank resources, which may undermine public trust (Cadigan et al., 2014; Cadigan et al., 2013; Klingler et al., 2022). However, RbG approaches raise issues concerning the involvement of participants (Corbin et al., 2018; Mascalzoni et al., 2021; Minion et al., 2018). Disclosure concerns have been explicitly

highlighted because the disclosure of genetic information is moved to the invitation phase (Beskow et al., 2012; Beskow et al., 2010; Beskow, 2012). Thus, by inviting prospective study participants to an RbG study, they may incur partial or potential disclosure of their genetic information, possibly without being aware of its implications or without providing their personal decision to participate in these types of studies, if the possibility of participating in RbG was not clarified nor asked during the original consent process. The challenges of ethically managing recall and consent require careful assessment in various contexts, such as patient cohorts and healthy population cohorts, where participants' expectations can differ significantly (Heinzel et al., 2022): while patients might anticipate being contacted to gain deeper insights, the same might not hold for healthy individuals.

Due to these ELSI challenges, policies for guiding the research are required. As part of this policy development, empirical research can contribute to identifying both issues and their solutions (Mwaka et al., 2021) (Bergner et al., 2014; McGowan et al., 2018; Pervola, 2018; Rutakumwa et al., 2019). While policies that govern participant data and novel study designs, such as RbG in biobanks, need more uniformity, there is no one-size-fits-all solution for such policies (Henderson et al., 2013; Lemke & Harris-Wai, 2015). Stakeholder involvement and engagement have been used to provide 'contextual evidence' and inform specific practices and research (Barry & Edgman-Levitan, 2012; Carman et al., 2013; Fleurence et al., 2013; Hoffman et al., 2010; Krahn & Naglie, 2008;

Lemke & Harris-Wai, 2015; O'Haire et al., 2011; Puddy & Wilkins, 2011). Further empirical research can facilitate the development of evidence-based guidelines informed by the experiences and opinions of stakeholders (Beskow & Burke, 2010; Lemke & Harris-Wai, 2015).

The present study investigated challenges of RbG communication strategies and participant preferences for disclosure approaches to inform the development of the Cooperative Health Research in South Tyrol (CHRIS) study's policy regarding RbG research. The CHRIS study is an ongoing longitudinal, population-based cohort study in Val Venosta/Vinschgau, Italy (Pattaro et al., 2015). RbG studies have been conducted within the CHRIS study since 2018. We conducted a multistage empirical study that aimed to understand the perspectives of research participants and other stakeholders, including researchers and study personnel, on the RbG approach in the context of the CHRIS study. This study aimed to contribute to the debate on ELSI issues in RbG and to offer elements for policy building in RbG that may be generalisable to other contexts.

Methods

Aim

With this study, we investigated research participants' views and preferences regarding communication and disclosure strategies in RbG approaches through quantitative methods. Additionally, we explored stakeholders' views (researchers and study personnel) on

communication and disclosure challenges in RbG approaches with a qualitative method. Considering their perspectives and experiences, this study aimed to understand crucial aspects of RbG communication strategy, inform CHRIS RbG disclosure policies and provide generalisable recommendations for best practices.

Study context

RbG studies in the CHRIS study

In the past two decades, research into neurogenetic diseases, such as Parkinson's disease (PD), has highlighted a range of causes, clinical manifestations, variations in populations, and increasing incidence and prevalence (Klein et al., 2007; Simon-Sanchez et al., 2009; van der Heide et al., 2021). Variants in the Parkin (PRKN) gene can cause genetic PD in homozygous individuals (Klein et al., 2007; Lesage et al., 2008; Simon-Sanchez et al., 2009). While evidence suggests that the heterozygous PRKN variant can increase the risk of some clinical symptoms related to PD or that it might be one of the potential genetic risk factors for PD, the relationship between heterozygosity in these genes and the development of Parkinsonism is not entirely clear and may depend on other factors (Castelo Rueda et al., 2021; Li et al., 2020; Zhu et al., 2021). Further research is required to clarify the degree to which heterozygous carriers of a recessive variant (e.g., in PRKN) are at an increased risk of PD.

Within the ProtectMove project ("ProtectMove," 2023), the CHRIS study conducted an RbG study in August 2018 (RbG1), followed by a subsequent RbG study in April 2022 (RbG2). Both were conducted at the CHRIS study centre in Silandro (Italy). These studies aimed to assess carriers and noncarriers of heterozygous PRKN variants phenotypically.

RbG2 study communication strategy

In RbG2, the study design was similar to the one of RbG1 (Mascalzoni et al., 2021). The communication strategy that was used was similar to the one used in RbG1 (Roberta Biasiotto et al., 2023) and included the followings:

- Participants were invited through a letter and were provided with comprehensive and detailed information about the study, including its objectives, study design (see Figure 1 for a detailed overview of how study design and objectives were framed), eligibility criteria, participant selection process, logistical details, examination procedures, associated risks and benefits, participant rights, informed consent process, voluntariness, data privacy, ethics approval, funding of the project.

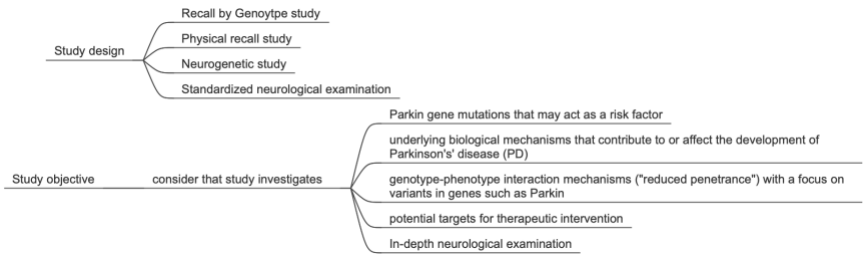


Figure 7: How the study design and objectives were framed in the letter inviting research participants.

- Participants were communicated the disease under investigation, PD, and the specific genetic variant under investigation, PRKN. They were not communicated the individual carrier status.
- In the CHRIS study's dynamic informed consent, participants can choose – and change over time – what types of genetic results they would like to receive in case Return of Research Results (RoRR) is applicable (Mascalzoni et al., 2022). The reasons for non-disclosure of the individual carrier status and the RoRR strategy (no return of research results) was explained: considering that carrying PRNK in heterozygosis was not associated with any known clinical benefit (R. Biasiotto et al., 2023; Mascalzoni et al., 2021) and in line with established disclosure policy, the individual carrier status for the PRKN variant was not disclosed in either the initial invitation or after the study. To address previous findings by Kösters et al. (2019) on participants' expectations or possible misconceptions regarding the return

of unsolicited results, it was crucial to provide clear and transparent information on this implication of participation. No compensation was foreseen.

- For further information and clarification, dedicated CHRIS center contacts (phone number and email) were made available.

Study Design and Methods

This study was designed as a multistage empirical investigation, including quantitative and qualitative approaches. Building upon previous findings (R. Biasiotto et al., 2023; Kösters et al., 2019; Mascalzoni et al., 2021; Tschigg et al., 2022), we designed the following steps:

1) Survey with CHRIS participants who participated in the RbG2 study, aiming to get insights into participant experience with the study process and views on disclosure related to a specific type of variant and disease (in the context of an RbG investigation on heterozygous PRKN variants and PD);

2) Focus group discussion (FGD) with researchers with experience in RbG approaches, aiming to understand researchers' perspectives on essential aspects, difficulties, and concerns related to the design of RbG studies.

3) FGD with CHRIS study personnel investigating their experience on the practical aspects of the RbG approach and direct contact with participants throughout the informed consent process and the overall study.

4) Cross-sectional online survey submitted to a sample of the CHRIS cohort to investigate research participant preferences regarding possible RbG disclosure policies.

Results obtained in Step 2 and 3 contributed to the design of the survey used in Step 4. In the Discussion, we integrated quantitative and qualitative findings through a narrative approach (Fetters et al., 2013) and discussed the findings in relation to developing recommendations for best practices and policy adjustment on RbG studies.

Step 1: Survey with RbG2 study participants

In April 2022, a survey was administered to participants of the CHRIS study who had participated in the RbG2 study. The questionnaire, available in German and Italian (shown in English in Supplementary Information investigated the following areas: satisfaction with the RbG study design, experience with PD, willingness to receive information about carrier status, self-assessment of noncarrier likelihood, and essential aspects of genetic research participation. The survey was completed online at the study centre using the LimeSurvey platform, with study personnel available to assist participants and address any questions. Quantitative data were analysed using descriptive and statistical methods in Excel ("Microsoft Excel Spreadsheet Software | Microsoft 365," 2023), while open-ended questions were analysed through qualitative content analysis (Cresswell, 2014; *Research*

Design, 2023) in Italian and German. The results were then translated and discussed with all the authors.

Steps 2 and 3: Focus group discussions

We conducted two FGDs in June 2022. The overall aim was to discuss RbG-specific ELSI challenges as perceived by study personnel and researchers in the process of the RbG study. We followed relevant guidelines for conducting, analysing and reporting findings (Wong, 2008).

Step 2. FGD with study personnel: Recruitment and data collection

In June 2022, an FGD was conducted in person with CHRIS study personnel at Silandro Hospital's CHRIS centre. The inclusion criterion was RbG study experience in the CHRIS study.

We developed information material to clarify the terminology related to RbG approaches and four hypothetical versions of an RbG study invitation letter, which differed in the level of detail. The discussion guide and the translated exemplary invitation letters are shown in the Supplementary Information. The FGD was conducted in German (the mother tongue of the FGD participants and the moderator), moderated by one author (KT), and observed by another author (MD). The FGD lasted approximately 90 minutes.

Step 3. Focus group discussion with researchers: Recruitment and data collection

In June 2022, an FGD was conducted online with researchers with experience in RbG approaches within the CHRIS study and the ProtectMove study ("ProtectMove," 2023). For the sampling strategy, we used a combination of purposive and snowball sampling (Singh & Moodley, 2021). Participants were recruited by email, and the FGD, conducted in English, explored research-related aspects of RbG approaches. The inclusion criterion was experience with the design or ethical assessment of RbG studies. The discussion guide was developed from discussions among colleagues and is shown in the Supplementary Information. The FGD, led by one author (KT) and observed by another (DM), lasted approximately 90 minutes.

Data analysis

Audio recordings of the discussions were transcribed for analysis. KT analysed transcripts using qualitative content analysis (Cresswell, 2014; Hsieh & Shannon, 2005; *Research Design*, 2023), and the results were discussed with the authors. Descriptive summaries of the main findings were produced and selected quotes (originally in English or translated into English) to illustrate the key considerations were included. The analysis was performed in the respective language of the FGD.

Step 4: Survey with CHRIS baseline participants

We developed a cross-sectional survey that included extensive information material through an iterative review process with research group leaders who had conducted research within the CHRIS study and its coordinator. The answer choices were informed by the results obtained in Steps 1 to 3 and previous research (R. Biasiotto et al., 2023). Furthermore, we used 'think aloud' methods (Kernebeck et al., 2022) to test the content of the information material, survey questions, and answer choices with the study personnel and discussions with the CHRIS study coordinator regarding comprehension and adequate language for the participants.

A sample of 1,721 CHRIS baseline participants was invited to answer an online questionnaire hosted by LimeSurvey ("LimeSurvey — Free Online Survey Tool," 2023). The sampling strategy was designed to recall participants from the CHRIS baseline study who had also taken part in the subsequent follow-up (CHRIS 2) due to their updated consent. Specifically, we sought to include CHRIS 2 participants who had not been previously approached for participation in recent sub-studies to avoid possible participation overburdening. The survey was available in German and Italian according to each respondent's language preferences. Respondents had two weeks to complete the survey in April 2023.

The following aspects were the focus of this quantitative investigation: feelings regarding the level of comfort about RbG

invitations and disclosure strategies, the importance of potentially receiving specific information before and after participation, preferences for disclosure strategies concerning different types of genetic variants, and feelings about a hypothetical RbG approach with no disclosure of study details. The questionnaire (provided in Supplementary Information) comprised closed- and open-ended questions.

Data collection and analysis

Data collection occurred in April and May 2023. Only fully answered questionnaire response were considered for the analysis. Demographic data were used as descriptor of the sample.

We used Excel ("Microsoft Excel Spreadsheet Software | Microsoft 365," 2023) and SPSS ("SPSS Software," 2023) for the descriptive statistics of the quantitative data in the form of Likert-scale questions and single- or multiple-choice questions. We used qualitative content analysis for the open-ended questions that were coded and categorised (Hsieh & Shannon, 2005).

Results
Step 1. Survey With RbG2 Participants

Characteristics of respondents

All of the RbG2 participants (N = 96) completed the survey after participating in the examinations in the study centre in Silandro. There were 53 male and 42 female participants aged 40–75 years. For one participant, data on gender and age were not available.

Satisfaction concerning different study processes, phases and materials

The vast majority of respondents (94 respondents, 97.9%) felt like their questions had been answered during the study process, and a very small minority felt like not all of their questions had been answered (2 respondents, 2.1 ~~08~~%). Similarly, most respondents felt well-informed about the study and were satisfied with the information provided and the overall experience of the RbG study process (Figure 2). The majority of participants had positive or very positive feelings about the invitation process (89 respondents, 92.7 %), the rationale behind the study (86 respondents, 89.6%), viewed the information material and the informed consent process positive or very positive (80 respondents, 83.3%). The study team, including doctors and non-doctor personnel, were positively perceived by the most.

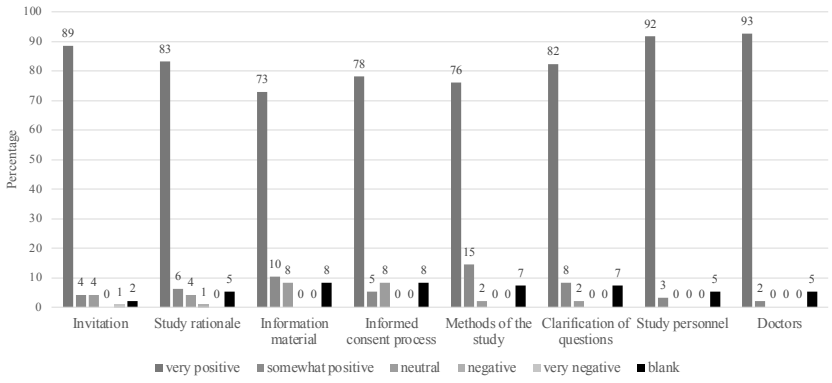


Figure 8: Satisfaction of respondents with the RbG study components.

Key considerations when participating in genetic research

In an open-ended question, 36 respondents (37.5%) clarified perceived priorities and most crucial aspects when participating in genetic research, including personal benefits, such as receiving results and findings and gaining insights into one's health (e.g., staying informed about test results, discovering abnormalities, learning about risks/prevention, acquiring relevant health information, and learning about incisive disease factors and control); and collective benefits, such as helping and contributing to science, research study and development of targeted therapies, with an adequate level of privacy and discretion.

Willingness to know the individual carrier status and reasons

Most respondents (68 respondents, 70.8%) were willing to know their carrier status, while a minority (20 respondents, 20.8%) did not want to know the information on the carrier status; and very few (8

respondents, 8.3%) expressed that they did not care about knowing their carrier status (Table 7).

Table 7: Willingness to know the individual carrier status clustered by gender and age group.

Gender	Sample size (n=)	Yes	No	I do not care
Female	42	29 (31%)	10 (11%)	4 (4%)
Male	53	39 (41%)	10 (11%)	3 (3%)
Total	95	68 (72%)	20 (21%)	7 (7 %)
Age groups				
40-49	31	22 (23 %)	7 (7 %)	2 (2 %)
50-59	45	32 (33 %)	8 (8 %)	5 (5 %)
60-69	14	11 (11 %)	3 (3 %)	0%
70-75	5	3 (3 %)	2 (2 %)	0%

Respondents' primary reason to know their carrier status was to prepare for the possible onset of symptoms and hereditary reasons (Figure 9).

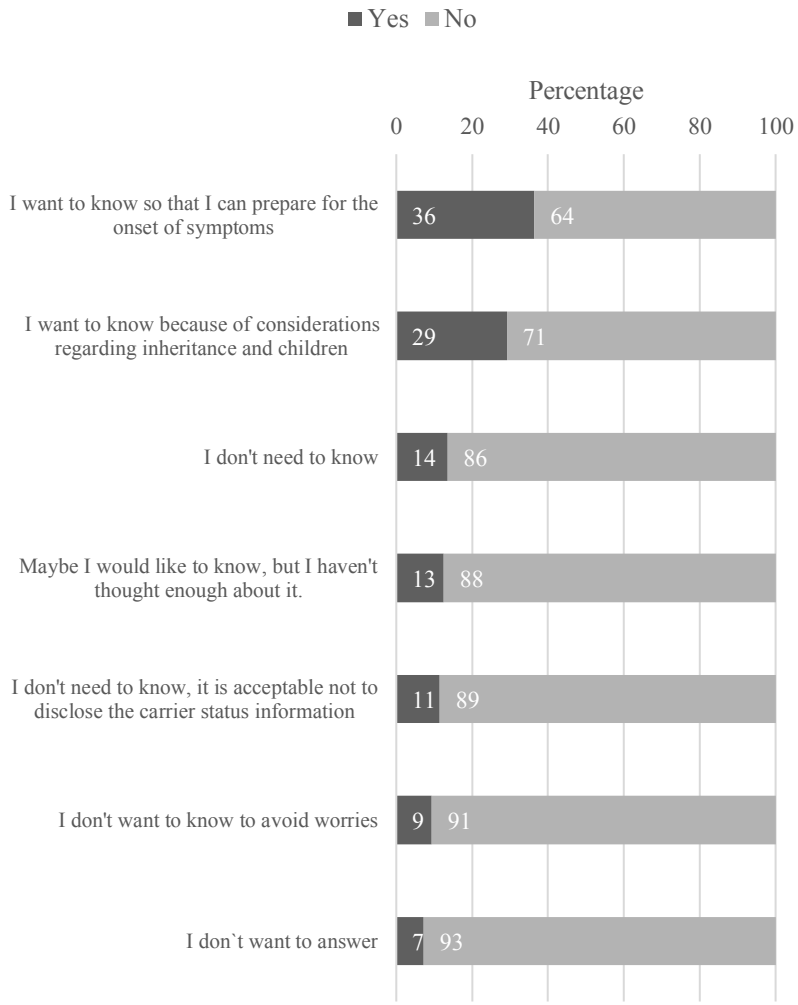


Figure 9: Motivation for wanting or not wanting to know one's individual carrier status based on expressed relatability to the provided reason.

Self-assessment of the likelihood of carrying the variant under study and experience with PD

Across all respondents, the average perceived probability of not carrying the PRKN variant in heterozygosis was recorded at 39.9%.

The respondent's perceptions of their likelihood not to carry the studied variant exhibited a spectrum of confidence levels (Figure 10). This range extended from pronounced assurance (response 100) to substantial uncertainty (response 0). The most frequently chosen likelihood is 50 (28 respondents, 29.2%), the median of all responses is 50, and the average is 39.9.

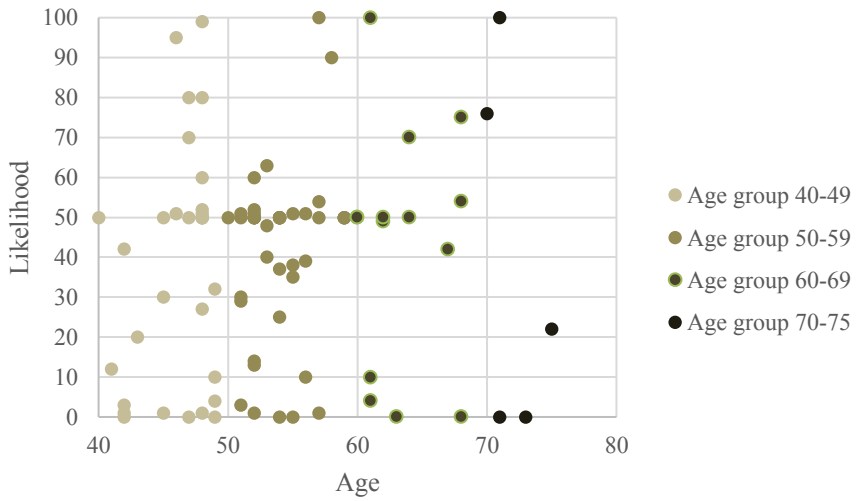


Figure 10: Self-assessment of the likelihood of not carrying the variant according to age.

Of the 96 respondents, 24 reported having experience with PD in their families; the rest reported no experience or being unsure, while one respondent did not want to answer the question. We did not find a significant effect of a familial history of PD or the decision of wanting to know one's individual carrier status.

Step 2. Focus Group Discussion with the Study Personnel

A total of six CHRIS study personnel participated in the FGD. The study personnel highlighted concerns about potential misunderstandings by participants and difficulty explaining the reason for the invitation without causing concerns. For example, they viewed the RbG study design based on matching carriers and non-carriers as confusing and potentially causing concerns related to a possible perceived increased risk of health issues:

> *The possibility of a disease is much more concrete. If you are selected by genotype to participate in a study, then the risk or the possibility is actually 50/50.* (*P1)*

To mitigate this concern, the study personnel emphasised the need to offer clarifications and address these concerns in the recall phase. They proposed strategies for ensuring the clear comprehension of information, and striking a balance between providing information and preventing information overload such as employing user-friendly electronic tools for communication (e.g., apps and websites). When discussing hypothetical invitations with different degrees of information and disclosure, it was unanimously agreed that the foremost critical information is the associated disease. They found that the best version explained the study design, rationale, and associated disease but did not disclose the specific genetic variant or individual carrier status. In their view, it is crucial not to overwhelm participants at the beginning with too many details;

instead, one should use a layered approach as regard timing and modality, for example, providing further explanations in a face-to-face setting. The concept of sensitivity, as the ability to be considerate of other people's feelings (expressed by the word *feingefühl*), was suggested for tailoring the disclosure and communication approach to the study context. The growth of the biobank, leading to more studies and more engagement, was perceived to deepen the relationship between the study personnel, doctors, researchers, and participants and to develop their role as partners:

> *[T]he follow-up studies are actually something nice because people feel like they are not studied only one time but studied more often and therefore become part of the research.* (*P3)*

The study personnel perceived that in-person explanations were valued by participants as a means of increasing awareness and genetic literacy concerning research in general and the specific disease under study in each substudy:

> *Yes, that direct communication in the field* [*in the study centre*] *is what makes the study so interesting because they put in the effort no matter if they get something [results or compensation] or not; they [the participants] would already come out a bit smarter about the situation.* (*P2)*

Step 3. Focus Group Discussion with Researchers

In Step 3, seven researchers with expertise in different fields and roles in research (i.e., epidemiologist, study coordinator, scientist, and ethics board member) participated.

For researchers, participants' perspectives and preferences were crucial to the design and implementation of RbG studies: considering participants' views would contribute to promote respectful and transparent engagement without objectification or misunderstandings about the implications of participation. Communicating complex scientific concepts in an understandable manner (e.g., transparent communication without overwhelming scientific jargon) was perceived as a challenge because of a lack of specific training in the field and the possible risk of unwanted medicalisation of healthy individuals. Sampling and recall strategies were deemed critical, highlighting challenges in identifying controls and managing participants' consent for follow-up studies. Debates arose regarding the disclosure of individuals' carrier status and the study objectives, with uncertainty complicating effective communication. The researchers agreed that clear communication is crucial but challenging when uncertainty exists about the utility or consequences of a particular genetic variant. They agreed with the difficulty of identifying generalised rules for disclosure so that case-by-case solutions would be required:

> *I think that it's really difficult to generalise. That is the type of disclosure because there are some*

> *diseases or some arguments that we just imagine epilepsy or dementia that are more delicate than others. And then you have to really define the communication also to the population that you are considering and these things. So, if you have to just suggest some things, it depends really on the case from the study that you are studying; there is not a general rule in my case.* (P2)

Regarding how to approach disclosure policies, some researchers suggested diluting or enlarging subsamples to ease burdens. Others emphasised the importance of participants' choice to have disclosure or concealment:

> *And of course, there are certain risks and benefits involved both in disclosure and concealment, but wouldn't you say that it should be the participant's choice whether they want to have disclosure or concealment? Of course, we have to kind of explain it to them well enough.* (P4)

The tailoring of approaches was focused on the timing of disclosure (i.e., the possibility of disclosing the carrier status after participation) and adhering to participants' preferences. Tailoring disclosure policies according to the specific case was perceived as necessary to avoid skewing the results. This could occur due to explicit or implicit knowledge of an individual's carrier status affecting their perception and performance in the RbG study.

Step 4. Large-Scale Survey with CHRIS Participants

Characteristics of CHRIS survey respondents and feedback

We obtained a response rate of 24.33%, from 417 respondents. After the removal of partial submissions, the final data set comprised 368 respondents for the analysis. Respondents were aged in the range of 29–90 years, while their median age was 52 years. Of the total number of respondents, 200 identified as female (54.3%), 141 as male (38.3%), and 27 (7.3%) did not answer or are missing because of a technical issue affecting the first survey respondents. Regarding languages, 98% and 2% filled out the questionnaire in German and Italian, respectively. Approximately 10% of respondents provided general feedback, which concerned:

1. Satisfaction and trust: a) appreciation for the opportunity to participate in the CHRIS study; b) positive experiences and comfort during the study; and c) expression of trust in the CHRIS study and team.
2. Suggestions for improvement: a) simplified language (replacement of complex medical terms with simple and understandable language); b) desire to receive findings and summary of aggregated results.
3. Interest in research and further participation: willingness to participate in future studies in general and on specific diseases.

Reception of RbG invitation and reasons

A total of 218 respondents (59.2%), expressed that they would feel comfortable in receiving the invitation to participate in the RbG study; 91 respondents (24.7%) were indifferent; and 53 respondents (14.4%) indicated that they were uncertain about how they felt regarding the invitation. Only two participants (0.5%) stated that they were not comfortable with the invitation, and three participants (0.8%) chose `other`.

The primary reasons for feeling comfortable were a positive experience with the CHRIS study and a desire to contribute to scientific knowledge and develop better therapies (Table 3). Feeling uncomfortable participating in a hypothetical RbG study was considered to be caused by no special reason (228 respondents, 58.1%) and worrying that something negative might be discovered about their or their family's health or genetic risk factors (94 respondents; 23.9%) (Table 8).

Table 8: Reasons for feeling comfortable or uncomfortable about participating.

Reasons for feeling comfortable		**Reasons for feeling uncomfortable**	
Answer	**N (%)**	**Answers**	**N (%)**
I had a good experience with CHRIS	128 (34.8)	No special reason	214 (58.2)
I would like to contribute to scientific knowledge and the development of better therapies	108 (29.3)	Worries about negative health/genetic findings for self/family	87 (23.6)
To gain knowledge about my health: like blood / urine tests in CHRIS Baseline	53 (14.4)	Other	28 (7.6)
To gain knowledge about the genetic risk factors for me or my family	40 (10.9)	Concerns about not comprehending the study details	20 (5.4)
I felt a sense of solidarity for society and future generations	26 (7.1)	I would rather not answer	15 (4.1)
No special reason	7 (1.9)	Unwillingness to invest time and effort	4 (1.1)
I felt it was a duty	3 (0.8)	Disinclination towards smaller studies	0 (0)
Other	2 (0.5)		
I would rather not answer	1 (0.3)		

Preferences for type of information to be disclosed at invitation

Most respondents indicated they wanted information in the invitation letter related to the following aspects, in decreasing order: the return of clinical results (89.0%), the disease under investigation (87.5%), genetic risk information (85.4%), genetic variant of interest (76%), availability of consultation with healthcare professional (68.1%), and study rationale (50.2%) (Table 9).

Table 9: Participant preferences for information in the invitation letter before the RbG study.

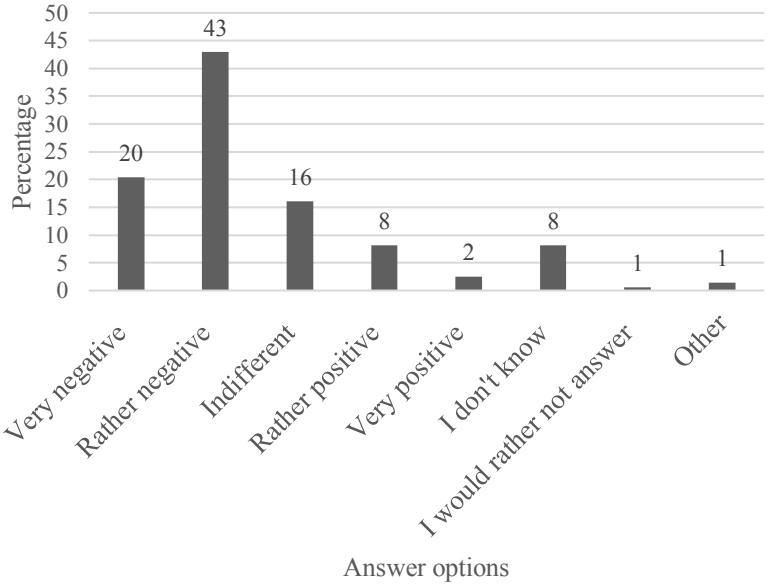
	Preferences for disclosure at the invitation			
Type of specific information	**Would definitely like to know**	**Indifferent**	**I'd rather not know**	**I prefer not to answer**
Which disease is being investigated	326 (88.6)	35 (9.5)	5 (1.4)	2 (0.5)
Which genetic variant is being studied	284 (77.2)	77 (20.9)	5 (1.4)	2 (0.5)
The reason why some CHRIS participants are invited, and others are not	188 (51.1)	164 (44.6)	10 (2.7)	6 (1.6)
Whether clinical results are returned (e.g. blood results)	333 (90.5)	33 (9.0)	1 (0.3)	1 (0.3)
Whether information about genetic risk factors is offered	322 (87.5)	40 (10.9)	5 (1.4)	1 (0.3)
Whether a doctor is available to ask questions	254 (69.0)	113 (30.7)	0	1 (0.3)

Reception of invitation without specifics

As shown in Figure 11, most respondents expressed negative feelings (Very negative: 75 respondents, 20.4%; Rather negative: 158 respondents, 42.9%) about receiving an invitation without detailed information about the genetic variant and the disease under investigation. On the other hand, some had positive or highly

positive feelings (Rather positive: 30 respondents, 8.2%; Very positive: 9 respondents, 2.4%) about this approach. Others expressed uncertainty (30 respondents, 8.2%) or preferred not to provide an answer (2 respondents, 0.5%).

Figure 11: Overview of the respondents' feelings about the invitation without specifics in the invitation letter



Approximately 18% of the respondents (66 responses) explained their choice in the open-field text, from which we identified the following considerations:

1. Desire for information: Respondents expressed a clear desire to be informed about any potential diseases or health

conditions ('I support genetic research, but I want to know what it is for and about which disease'), while others expressed indifference or a lack of interest in being informed about diseases.

2. Concerns about lack of information: Participants expressed a range of emotional responses, including worry, anxiety, concern, fear, and increased uncertainty, to not being informed about the genetic variant and associated disease (e.g., 'I would immediately worry because I would think that there is a risky situation that I am not yet informed about').
3. Acceptability of non-disclosure: Some respondents mentioned the role of ethical and legal aspects when deciding whether to provide information about diseases (e.g., 'I would welcome being informed, but if the committee cannot inform due to ethical and legal reasons, then I accept that').
4. Trust in the research and scientific process and desire to contribute: Respondents expressed a willingness to contribute to research (e.g., 'I am willing to participate if it is beneficial for research') and trust in the researchers (e.g., 'I trust the scientists conducting the study').
5. Importance of transparency and communication: Respondents emphasised the importance of transparency in the study, especially regarding using their data and avoiding disinformation or feeling objectified (e.g., 'I want to know what is being researched with my data').

6. Expectation and reciprocity: Participants expressed the desire to contribute to research but also expected some benefit or feedback regarding the results or findings of the study. Several respondents expect a level of reciprocity for their participation, indicating that if they contribute to research, they should receive valuable information in return.

Disclosure of individual genetic information after an RbG study: feelings, concerns, and impact

The majority of respondents (60-82%) felt comfortable potentially receiving information about their genetic data (disclosure of individual carrier status) for different types of genetic variants (diseases-causing/pathogenic genetic variants, probably pathogenic genetic variants, benign genetic variants, protective genetic variants, or genetic variants of uncertain clinical significance) after participating in an RbG study (Figure 12). The highest level of comfort was reported for protective genetic variants (82%), while the lowest was reported for genetic variants of uncertain clinical significance (60%). By contrast, a small percentage of respondents reported feeling uncomfortable (1–6%), feeling indifferent (7–16%), or not knowing how they felt (6–12%) about receiving information about their genetic data and variants after the study

(Figure 4). Approximately one-third of respondents justified their choices in an open-text field.

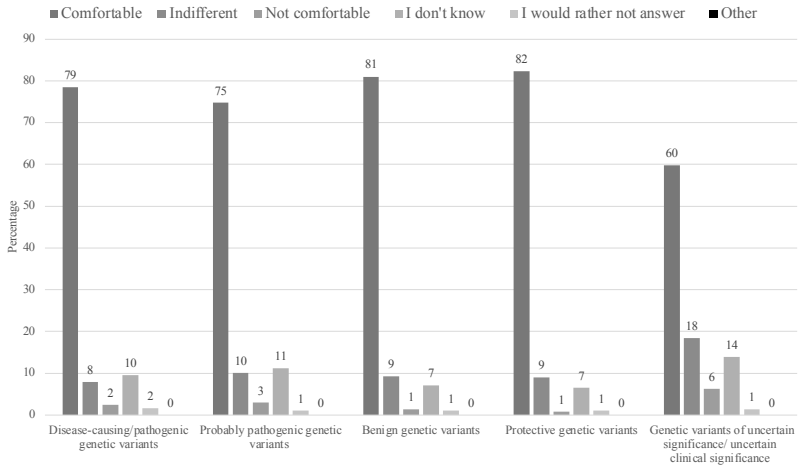


Figure 12: Feeling comfort in receiving individual genetic information (disclosure of carrier status) for various types of genetic variants after participating in RbG studies focused on different genetic variants.

Approximately 7% (23-30 respondents) of respondents wrote in the open field to explain motivations or concerns about the different variants. We identified the following considerations shared for all the types of genetic variants:

1. Importance of being informed: A shared belief existed that receiving information about one's genetic characteristics is essential. The participants expressed that being informed would allow for preventive measures, early detection, or appropriate actions.

2. The desire for detailed descriptions: Participants emphasised the need for clear and comprehensive descriptions of the genetic variants and their implications. They valued receiving informative and understandable information, especially regarding potential disease risks or preventive measures.
3. Preference for consultation with healthcare professionals: Some respondents preferred to consult with healthcare professionals to understand their genetic variants' significance better. They believed professional guidance would be essential for accurately interpreting the information and making informed decisions about their health.

We found differences in the level of interest, perceived relevance to personal health, emotional impact, and understanding according to the type of genetic variant under investigation (Table 10).

Table 10: Overview of the responses regarding different types of genetic variants.

	Disease-Causing/ Pathogenic Variants	**Probable Pathogenic Variants**	**Benign Variants**	**Protective Variants**	**Genetic Variants of Uncertain Significance**
Level of interest	High	High	Lower (compared with disease-causing and probable pathogenic variants)	Lower (compared with disease-causing and probable pathogenic variants)	Mixed responses (including disinterest, concerns about uncertainty, and desire for clear results)
Perceived relevance to personal health	Highly relevant	Relevant	Less relevant	Less relevant	Relevance was uncertain, with varying degrees of importance attributed to these variants
Emotional impact and responses	Worry, anxiety, and the desire for additional cautiousness	Worry and the desire for additional precautions	Provision of reassurance and reduction of worry	Provision of reassurance and reduction of worry	Mixed responses (expressing worry or a desire for clearer information)
Perceived level of understanding of implications	Well-understood and acknowledged to have significant implications	Some uncertainty regarding their exact implications; professional guidance should be sought for interpretation and understanding	Understood as indicating a lower risk or no significant health impact	Potentially helpful in guiding lifestyle choices or behaviors	Professional guidance should be sought to interpret and understand the significance

Disease-causing and probable pathogenic variants evoked a higher level of interest, while benign and protective variants were considered less relevant but offered reassurance or potential benefits. Variants of uncertain significance elicited mixed responses, with some participants desiring more evident results and others exhibiting disinterest or concerns about uncertainty.

Discussion

This study was part of a broader multistage investigation within CHRIS and the ProtectMove project, which included a feasibility assessment and stakeholder engagement (Mascalzoni et al., 2021), and an empirical study with CHRIS participants who participated in an RbG study on Parkinson's disease (RbG1) (R. Biasiotto et al., 2023) as earlier steps. By surveying participants of a second RbG study focused on the assessment of carriers of heterozygous PRKN variants and noncarriers from the CHRIS cohort (RbG2) and a cross-sectional survey with a sample of CHRIS participants without previous experience of RbG approaches, we gained insight into participant perspectives and disclosure preferences. These were enriched by the communication and disclosure trajectory considerations that emerged during two focus groups, with researchers and CHRIS personnel. This study incorporated the obtained empirical results into considerations for a balance between researchers' needs and fundamental legal and ethical guidelines, and recommendations for best practices on RbG policy development.

Participant expectations on communication and preferences for disclosure

Decisions on disclosure and RoRR can be facilitated if researchers, study personnel, and the review board are aware of participants' expectations through empirical research or ongoing engagement and

tailor the plans and policies accordingly. In the large-scale survey (Step 4), most respondents expressed negative feelings about receiving an invitation without detailed information (Figure 11). They would want to be informed upfront principally (>85%) about the return of clinical results, the disease being investigated, and genetic risk factors (Table 9) thus showing a keen interest in the health implications of the study. Participant expectations of information aligned with expectations of transparency, reciprocity, and trust were also found in other studies (R. Biasiotto et al., 2023; Minion et al., 2018).

Disclosure of carrier status and context

As observed in another RbG study (Nurm et al., 2022), we identified a positive attitude toward the disclosure of carrier status in both surveys. In Step 4, participants reported feeling generally comfortable about disclosing individual genetic results after participating in an RbG study (Figure 4). However, different genetic variants with differing impacts on health were deemed to be received with different interests and need for interpretation of implications. When considering the specific variant under investigation in RbG2 (PRKN in heterozygosis, which could increase the risk of some attenuated PD clinical symptoms), most participants were willing to know the individual carrier status (Table 1) because they perceived this awareness to be beneficial due to heredity and potential onset of symptoms considerations (Table 2). In a previous empirical study embedded in a similar RbG (RbG1),

the nondisclosure of the PRKN variant carrier status was generally deemed acceptable, and participants were okay with genetic research results not being returned to them as they perceived their value within the research context only (R. Biasiotto et al., 2023). The primary considerations for the acceptability of non-disclosure of PRKN carrier status included the perceived low relevance for the personal health (R. Biasiotto et al., 2023). Even though the RbG1 and RbG2 studies share the main focus, the participant sample differed regarding age (older in RbG2), the embedded empirical studies used different approaches (mixed method in Biasiotto et al., 2023, survey in this study) and different investigations (e.g., acceptability of non-disclosure was not explored in this study), thus possibly reflecting the different results of these studies. The willingness of participants to know their carrier status, primarily driven by concerns for potential clinical symptoms and hereditary considerations, emphasizes the importance of providing relevant health information. Notably, familial history of PD did not significantly impact participants' likelihood assessments or their willingness to know their carrier status.

A recent study in Italy has reported that most patients expressed a desire to be informed about any gene variant, including those that may not be clinically actionable (Godino et al., 2021). Another study reported that participants were confident in using the individual results from whole genome sequencing (WGS) studies to prevent future disease and believed in the value of even uninterpretable information, among other factors that were motivated by wanting to

contribute to their health positively or that of their relatives (Facio et al., 2013). As observed in other studies, collecting expectations regarding the communication of results from WGS is crucial for avoiding disappointment (Suckiel et al., 2021). According to stakeholder perspectives, providing research participants with their results demonstrated respect for their autonomy and interests (Singh & Moodley, 2021; Tindana et al., 2020).

Researchers determine the process of recalling and the decision to offer individual genetic results and how to disclose them, often in consultation with institutional or external ethical review boards, where many contextual factors are considered. Decisions on disclosure and RoRR can be facilitated if researchers are aware of participants' expectations through empirical research or ongoing engagement and tailor the plans and policies accordingly. Participants might want to know if they have a genetic risk of a particular disease; however, a worry exists that such information, with or without clinical utility, could lead to undue anxiety, stigma, or discrimination (Beskow, 2017; Beskow et al., 2004; Beskow, 2012; Bledsoe et al., 2013; McGuire & Lupski, 2010). There are diverging views and discussions on how to define categories (from clinical to personal utility), which contextual factors should be prioritised in the assessment, what should be disclosed, and whether ethical obligation takes precedence over preferences (Beskow & Burke, 2010; Cassa et al., 2012; Matsui et al., 2021). We found that case-by-case solutions would be required from the researchers' perspective (depending on the utility of the information, the nature

of the disease, the study design, and participants' preferences). Results on the impact and interest of different genetic variants disclosure (obtained in Step 4, Table 10) may clarify the priority criteria according to participants' perspectives. As with good practical research decisions, ethical judgement requires contextual knowledge (Hammersley, 2009), and context matters when deciding on whether and how to offer individual genetic research results (Beskow & Burke, 2010; Beskow & Smolek, 2009; Bledsoe et al., 2012).

Navigating carrier status disclosure

A key focal point of the ongoing discourse surrounding RoRR is how RbG research methodologies impact the level of obligations. This is crucial to consider, as in numerous cases, the usual criteria or thresholds for actionability of the carrier status information may not be satisfied (Beskow et al., 2012; Beskow et al., 2010; Budin-Ljosne et al., 2013). In addition, a coordinated best practice has yet to be proposed regarding how and when to disclose or communicate the carrier status of genetic variants with unknown actionability or utility to participants. Before disclosing any genetic variant in an RbG study, evaluating whether it meets the disclosure criteria according to the guidelines, for example, provided by Matsui et al. (2021) is crucial. Information and definitions for the respective utility, from public health, clinical, and personal viewpoints, are crucial when assessing whether to disclose the carrier status (Bunnik

et al., 2011). According to Cassa et al. (2012), recommendations for evaluating the responsibility for communication to a participant include assessing various factors, such as the strength of association or treatment options. Still, if one or more of these factors are unknown or missing, the responsibility to disclose is indicated by 'unknown' (Cassa et al., 2012). A previous study by Kösters et al. (2019) in the CHRIS context investigating opinions of general practitioners and the genetic counselling service in Bolzano emphasised the need for clinical validation before returning research results. The genetic counselling service expressed support for participant autonomy in disclosure decisions and highlighted the potential for collaborative projects on genetic-related disorders, contingent on appropriate understanding and consent from individuals.

Notably, knowing one's carrier status could provide essential benefits, including early detection and intervention for potential health issues, as reported by RbG2 participants. A study examined the effects of the RbG study approach on participants' assessments several years after their genetic findings about familial hypercholesterolemia had been disclosed. By comparing recalled group characteristics with those of unrecalled groups with similar genetic profiles, the authors identified that participants' knowledge of their carrier status significantly affected the outcomes (Nurm et al., 2022).

How to tailor communication

Tailoring invitation and information material to participant preferences for disclosure

To effectively tailor communication, it is crucial to consider participant preferences for disclosure. We identified challenges related to designing the invitation letter and study-related materials, particularly in terms of transparency and managing expectations as observed in other studies (Leitsalu et al., 2021; Leitsalu et al., 2022). In RbG studies design, legal obligations, such as disclosing the study's nature and purpose, can be perceived differently depending on how the information is presented. Different ways of framing the information regarding an RbG2 study may result in different receptions and perceptions by the invited participants. Participants in Step 1 reported satisfaction with the information provided before and during the specific RbG study on PRKN and PD (RbG2) as specified in the study context. We incorporated these frames into the communication strategy so that participants are provided with a clear and comprehensive understanding of the study's design, objectives, and examination process. This approach aimed to enhance participant comprehension, comfort, and satisfaction throughout their involvement in the research.

In a sort of feedback loop, participation and engagement may result in increased health and scientific literacy (as suggested in previous studies (Beskow et al., 2012; Beskow et al., 2010; Budin-Ljosne et

al., 2013; Leitsalu et al., 2022), which, on the other hand, may benefit the understanding of future studies, as implied by the study personnel in the FGD (Step 3).

In the FGDs, concerns regarding framing was also presented as particularly challenging because of difficulties in providing participants with clear and understandable explanations of the study design, eligibility criteria, and utility and consequences of carrier status awareness (especially in cases of scientific uncertainty). Other identified difficulties lay in avoiding overburdening participants, preventing invitation fatigue and communicating about genetic variants without medicalising healthy individuals, and implications of genetic information at the familial level. Echoing findings from earlier studies (Deverka et al., 2012; O'Haire et al., 2011), we suggest that employing consistent terminology throughout interactions with participants and stakeholders would be beneficial for clear and effective communication over different disclosure strategies and implications.

To tailor information material to different preferences, it is crucial to consider participants' attitudes towards the disclosure of their carrier status. On the one hand, transparency is crucial for ensuring fully understanding and informed decisions about participation, and realistic expectations about the RoRR and study's outcome (Leitsalu et al., 2022). On the other hand, transparency regarding the study's purpose and participation eligibility should not be at the expense of the individual's (or relative's) right not to want to know genetic information (Beskow, 2017; Beskow et al., 2012; Beskow et al.,

2011). Several epistemic and other problems arise in assessing people's preferences and using them in biobank policies (Hausman, 2006; Parker, 2012). While the CHRIS study participants seemed interested in receiving information on the individual carrier status regarding different types of genetic variants, overall, there were various motivations for the matter, encompassing the perceived relevance for health, emotional impact, and implications. Accordingly, communication strategies for RbG studies could be based on previously defined choices on disclosure which accommodate different preferences and may be changed over time. A system providing participants with options to receive or decline personal genetic information may be implemented within dynamic consent models that enable participants to choose whether they receive specific genetic information in the recall. Using multimedia interfaces could allow participants in a long-term dialogue to receive precise information beyond traditional consent processes as well as improve comprehension while meeting requirements for transparency (Baker et al., 2016; Beskow et al., 2015; Budin-Ljosne et al., 2017; Sonne et al., 2013). This tool may be designed to provide supplementary materials to explain technical terms and concepts in plain language, regarding specific aspects of the RbG approach, such as the potential implications of the eligibility and disclosure possibilities to each specific RbG study; degrees of specificity regarding study details to enable tailored communication. Nevertheless, such a tool would only be helpful if

individuals can and want to access and engage with it (Teare et al., 2021).

Personal contact and balanced involvement

A large part of the satisfaction reported by participants in the large-scale survey (Step 4) was related to familiarity, comfort, and the professional conduct of the CHRIS personnel. Previous studies have recommended the possibility of participants being recontacted by someone who is 'trusted', 'familiar', or 'known' to them to enhance participant satisfaction and comfort (Beskow et al., 2012; Budin-Ljosne et al., 2013). Providing a welcoming environment, respectful and empathetic attitudes, and personalised interactions becomes crucial in contributing to a positive research experience and engagement. In parallel, a coordinated and balanced communication strategy (with defined frequency and type of communication that participants can expect) based on less intrusive methods, such as online public communication, should be developed to ensure that participants do not become overburdened through their involvement. While such engagement methods are less intrusive in their informing and consulting functions, estimating their impact and uptake is challenging (Lemke & Harris-Wai, 2015).

Conclusion

This study consisted of a multistage empirical investigation that explored research participants' and other stakeholders' perspectives on RbG studies and aimed to inform the development of effective communication and disclosure strategies and policies.

Considering the empirical studies on RbG conducted so far, divergences exist between stakeholders regarding the ELSI of RbG studies, concerning, for example, the recall strategies and return of individual genetic research results (Beskow & Burke, 2010; Beskow, 2012). These divergences reflected heterogeneity in viewpoints and approaches to disclosure, communication strategies, and study-specific policies related to RbG. This divergence was particularly evident in areas such as recall strategies and the return of individual genetic research results, highlighting the necessity for tailored approaches to disclosure, communication strategies, and study-specific policies. Personal contact with trusted individuals and a balanced approach to participant involvement were identified as pivotal factors contributing to participant satisfaction and comfort. The role of study personnel in facilitating clear communication and addressing participant concerns emerged as a critical element for communication trajectories and informed consent processes for RbG studies. Furthermore, the study underscored the importance of crafting communication strategies that are sensitive to individual preferences, emphasising the need for clear and understandable explanations of study details.

Transparency, reciprocity, and trust emerged as critical pillars that participants highly value in the dissemination of study information.

Strengths and Limitations of the Study

We adopted a multistep approach, including various research methods and stages. This allowed a more nuanced understanding of the diverse considerations associated with disclosure in RbG studies, from specific (RbG2 study) to generalized situations (possible future RbGs with different types of variants), ensuring that the policy development process was informed by those involved in RbG studies, primarily by research participants, but enriched by contextual considerations of researchers and study personnel. However, given that this multi-step study occurred within the CHRIS context, our findings' generalizability may be limited. To strengthen future research in this field, we recommend including more and different ELSI experts (such as research ethics committee members, policymakers, and regulators), and research participants from different settings. This broader engagement will contribute to a more comprehensive understanding of the governance and oversight of biobanks in RbG research. Possible future investigations aiming to policy development may consider using other quantitative methods to detect preferences and extend these investigations to other contexts quantitively.

Authors' contribution

KT conceptualised and designed the surveys and FGD, conducted data collection, analysis and interpretation. All the Principal investigators of the Institute for Biomedicine and the Communication team were included in the review of the information material and content of the survey as this is part of the standard operating procedures at the Institute.

KT drafted the manuscript. All authors reviewed the manuscript, approved the final version and have agreed both to be personally accountable for the author's own contributions.

Chapter 4 – Discussion, Reflection, & Conclusion

This chapter offers a critical and comprehensive discussion that reflects the preceding chapters, drawing together key findings and insights. This chapter initiates with a focused reflection on the defined objectives, allowing for a coherent synthesis of the research results and observations throughout the PhD project. Subsequently, the discussion delves into the intricate ELSI challenges that have surfaced throughout the studies. Furthermore, the chapter addresses the implications of the research findings for disclosure, communication, and informed consent processes, shedding light on the potential refinements for future ELSI frameworks for RbG studies. Additionally, the discourse expands to explore the implications of the disclosure of genetic information, outlining how the research insights can inform strategies that facilitate effective and ethical disclosure practices. Lastly, this chapter discusses the outlook for future studies to establish broader ELSI frameworks.

Reflection on the Objectives and Key Findings

This study was part of a multistage investigation within CHRIS and the ProtectMove project designed to encompass several sequential steps to assess the research topic thoroughly. Through this comprehensive approach, we strive to shape the development of RbG and RoRR policies by integrating the views of participants and other stakeholders, addressing ELSI considerations, and balancing

them with researchers' needs and fundamental legal and ethical requirements, guidelines and aspirations.

In the first part of this multistage investigation, we identified, contextualised and discussed the ELSI of RbG studies in an international context through a scoping review. These challenges include the need for a consensus within the scientific community regarding best practices for different types of studies and appropriate strategies for disclosing, communicating and returning research results informed by participant preferences or by expert opinions and ethical guidelines. To further investigate some of these challenges and address the ELSI, we conducted several empirical studies with different stakeholders, which are crucial for the RbG environment.

Based on the empirical findings, a more informed approach to RbG studies in real-world settings can be developed, thereby ensuring effective communication and disclosure strategies. Sensitivity (*feingefühl*) has been identified as a facilitating lens through which recall, disclosure and communication strategies, as well as disclosure policies, can be tailored to the specific study characteristics and participants' perspectives and preferences. It refers to a nuanced and delicate approach to understanding and responding to the feelings, needs, and preferences of others in a particular situation. In various contexts, sensitivity emphasises the ability to empathise, perceive subtleties, and consider the impact of one's actions or words on others. In this research context, we highlight the importance of sensitivity to family dynamics and

implications and provide clear information based on the desired level of study-related details using tailored and context-specific communication strategies.

Moreover, within the scope of this research, the concept of sensitivity encompasses implementing strategies for systematically monitoring and gathering feedback from stakeholders throughout the research journey. These strategies should possess a level of sensitivity that enables potential misunderstandings or concerns voiced by participants to be identified.

In addition to sensitivity being a facilitating perspective, recognising distinct frames within information materials holds significance. This is because they highlight how communication strategies influence participants' perceptions and willingness to engage in RbG studies. Acknowledging these potential framings and their effects could ultimately enrich conversations during the information material design phase among the collaborating teams and ultimately for participants. Awareness and sensitivity regarding such dynamics may foster or ensure effective communication strategies that resonate with participants.

The influence of relational aspects and family dynamics emerged as an essential aspect across all perspectives—those of scientists, study personnel, and participants. One of the key takeaways from the results is the importance of recognising participants' autonomy within the context of family dynamics for making informed decisions about gene variant disclosure while considering potential familial impact. In this context, autonomy in the role of a biobank

donor/participant may be better understood from a relational perspective to acknowledge the significance of relationships between researchers, participants, and their families or friends in decision-making and the sharing of health-related data and research findings (Mezinska et al., 2020), thus recognising the blurred boundary of clinical care and precision medicine research in biobanks (Blumling et al., 2021; Kraft et al., 2018). This aligns with the specific context of the RbG study in CHRIS. In this context, both relational and individualistic dimensions of research participation require consideration because of the longitudinal and long-term character of the collaboration between researchers, study personnel, and participants; the family-based character of the cohort; and the aims of promoting autonomy and ensuring a trust-based engaged relationship with participants (Mascalzoni et al., 2021; Mascalzoni et al., 2022).

Discussion

This discussion is structured into three interwoven sections, each shedding light on crucial aspects of ELSI of RbG. The following three subsections discuss the implications and recommendations for communication, informed consent processes, and disclosure strategies for RbG studies.

Implications for communication strategies

This section delves into the challenges of designing effective communication strategies for RbG studies. It underscores the absence of a universal solution and the paramount role of contextual factors in shaping communication approaches. The section explores tailored communication strategies, the complexities of conveying study design and eligibility criteria, and the significance of empirical research in addressing ethical concerns and understanding participant perspectives.

The challenges in designing communication strategies for RbG studies underscore that there is no one-size-fits-all solution and that contextual factors are decisive to consider and tailoring the approach to the context. To address these challenges, this subsection discusses the significance of tailored communication strategies, the importance of considering contextual factors, and the need for empirical research to understand participant perspectives and preferences better.

Designing an RbG study poses significant challenges, particularly concerning communication strategies accompanying the disclosure and consent process. To address ELSI, it is crucial to consider the implications and challenges carefully from the outset of the study design (Beskow, 2017; Beskow et al., 2012; Budin-Ljosne et al., 2013; Mascalzoni et al., 2021). Researchers have acknowledged the paramount importance of clear communication; however, varying study designs and objectives necessitate a nuanced, case-by-case

approach tailored to the specific variant under study, considering its clinical implications and potential impact on participants' lives. By providing context-specific information, participants can make informed decisions about their participation and engage meaningfully in the research process. Communicating clear, understandable explanations of the study design and why a prospective participant is eligible was perceived as challenging for researchers.

Ensuring that participants fully grasp the implications of participating in the specific RbG study requires effective and sensitive communication, necessitating clear definitions and explanations of key terms. Empirical work can play a crucial role in addressing ethical concerns. It may also facilitate the monitoring of the study participants' understanding to avoid misconceptions about the research objectives or potential implications for their or their family's health, as other research studies have highlighted in this context (Beskow & Dean, 2008; Haga & Beskow, 2008; McGuire & Beskow, 2010).

Through empirical work accompanying the RbG study, we assessed the participant's perceived level of understanding and satisfaction regarding communication mechanisms and materials to ensure transparency and comprehension. To clarify potential misunderstandings, stakeholders highlighted the value of additional communication mechanisms, such as phone contact and time with the doctor, during the RbG study. This approach allowed participants to express their concerns and preferences, fostering a

more comprehensive understanding of the study's implications for them and, potentially, their families. By conducting rounds of feedback and an FGD with the study personnel, we collected insights highlighting the necessity of explaining the 'targeted' nature sensitively, implementing processes, and allocating time to clarify potential questions from the participants about the implications of study participation.

A potential partial solution to the abovementioned problem is a layered and staged model for managing the communication or disclosure of information gradually and comprehensibly. This model has already been demonstrated to ensure that participants receive the core information in a manageable way and to allow for an ongoing consent process, giving individuals more time to absorb the information gradually (Joly et al., 2014). This layered approach could facilitate the design and content of the invitation letter and study-related information materials, which were presented as challenges and seen by the study personnel and researchers as critical phases of the study design. The depicted steps involve strategic decisions regarding the essential information to be conveyed to participants, considering the study details illustrated in Figures 10 and 11 and determining the appropriate level of detail and framing of information. Figure 10 presents a comprehensive visual representation of the legal requirements related to communication and disclosure within the context of informed consent for a specific genetic research study. We used this representation to add the specific study details for the RbG2 study.

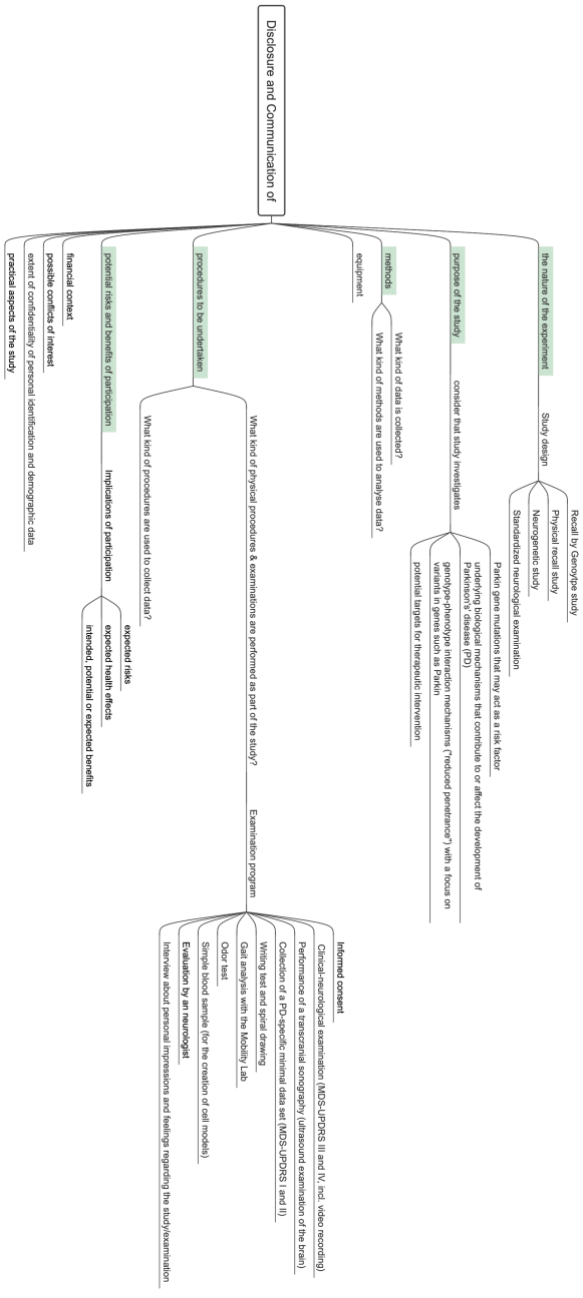


Figure 13: Overview of the legal requirements related to communication and disclosure within the context of informed consent for a specific genetic research study and the specific RbG 2 study details.

In addition, we identified challenges related to the invitation letters and study-related information materials associated with transparency and expectation management, as other studies by Leitsalu et al. (2021); Leitsalu et al. (2022) have also found. By exploring participants' responses to RbG study invitations with empirical research, RbG communications approaches can be more accurately tailored to ensure effective communication strategies considering participants' needs and preferences.

Throughout the design process of study-related information materials, researchers should also consider the potential implications and limitations of disclosure strategies and the framing effects that may influence participants' comprehension or decisions. It is critical to identify which framing effects challenge the validity of consent and how they can be eliminated (Bhutta, 2004; Chwang, 2016).

Here, we encountered challenges associated with discussions between different scientific experts who held various authorities over the 'appropriate simplification' (Hilgartner, 2016) regarding the content of the materials. Through iterative rounds of revisions with the PI, study coordinator, and communication teams, we shaped the content, with critiques noting either oversimplification or excessive complexity for participants. We aimed to strike a balance by performing a final check with the help of the study personnel, providing their views on what is an adequate level of detail and transparency for participants.

Furthermore, throughout the design process of the materials, we identified that for some legal requirements, such as the disclosure of the 'nature of the experiment' or 'the purpose of the study', different ways of presenting information on the study could be seen as different frames on the same information. This requires clarifications or discussions between experts. This clarification is highly relevant, considering that 84.8% of respondents to a European online survey for experts (researchers and professionals in the context of biobanks and other collections of biological samples) activities by Goisauf (2019) deemed that the information on 'the purpose and (future) objectives of the associated research' 'should be' provided.

Drawing on insights gleaned from empirical studies, we strategically refined the information material to enhance its efficacy in conveying the nature and purpose of the study. Recognising that different presentations of this information could be perceived through various frames, we engaged in thorough discussions among experts to ensure understanding. Consequently, there were minimal modifications in the content of the informational materials when transitioning from RbG 1 to RbG 2, specifically regarding the elucidation of the study's purpose and the process by which participants would receive results. We adapted the content for the RbG2 study for the bespoken topic to the following: '*The study is conducted for research purposes only. The results will not be communicated to you, as they are unsuitable for personal genetic counselling*'. This decision was made to avoid misunderstandings

about what relevant results should or could be. We did so to consider the finding that some participants assumed '*that everything was okay*' if they did not receive any other feedback from a previous CHRIS study on RoRR by Kösters et al. (2019). Despite the researchers' explicit clarification, some participants assumed the research team would proactively analyse their data to identify genetic variants associated with disease development.

When analysing the ELSI framework and information materials of RbG1 and RbG2, we roughly categorised the framings or 'different sides of the story' presented in Figure 14.

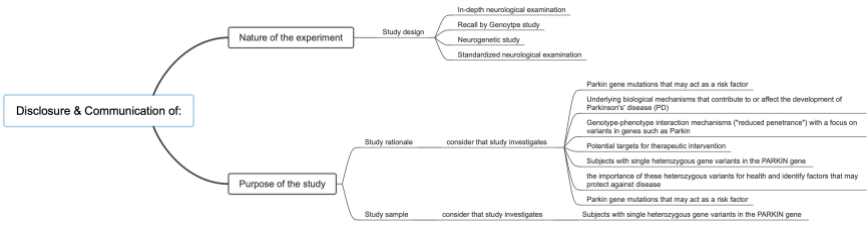


Figure 14: Overview of identified frames for the communication on the 'nature of the experiment' and 'purpose of the study'.

The identified different frames, illustrated in Figure 12, in the information materials highlight a different focus, from the role of the PRKN gene variant as a potential risk factor for the development of PD to a focus on investigating the potential targets for therapeutic intervention. However, the effect of framing in these situations or this context remains an understudied field of research.

Implications for Informed Consent Processes

This section examines the implications of informed consent processes in RbG studies. It explores the complexities of disclosure and consent, presents legal obligations and considerations, and suggests strategies for enhancing the informed consent process. The section also delves into challenges associated with autonomy and the right not to know while discussing factors supporting participants' autonomy in decision-making through carefully crafted consent processes and information materials.

For RbG studies, the informed consent process holds significant importance, particularly when RbG was not initially anticipated in the research design and, hence, not included in the original consent process. For RbG, careful consideration must therefore be given to the informed consent process, particularly to the kind of information provided about future research and whether it potentially involves RbG (Beskow, 2017; Beskow et al., 2012; Mascalzoni et al., 2021; Robinson et al., 2013). Accordingly, some scholars argued that if RbG were not foreseen at the outset, it would seem unacceptable to recall participants for RbG studies (Mascalzoni et al., 2021). However, as of now, there are no recognised ethical and legal standards for RbG in cohorts where RbG was not foreseen and was consequently also not included in the original consent process (Beskow, 2017; Beskow et al., 2012; Budin-Ljosne et al., 2013; Minion et al., 2018).

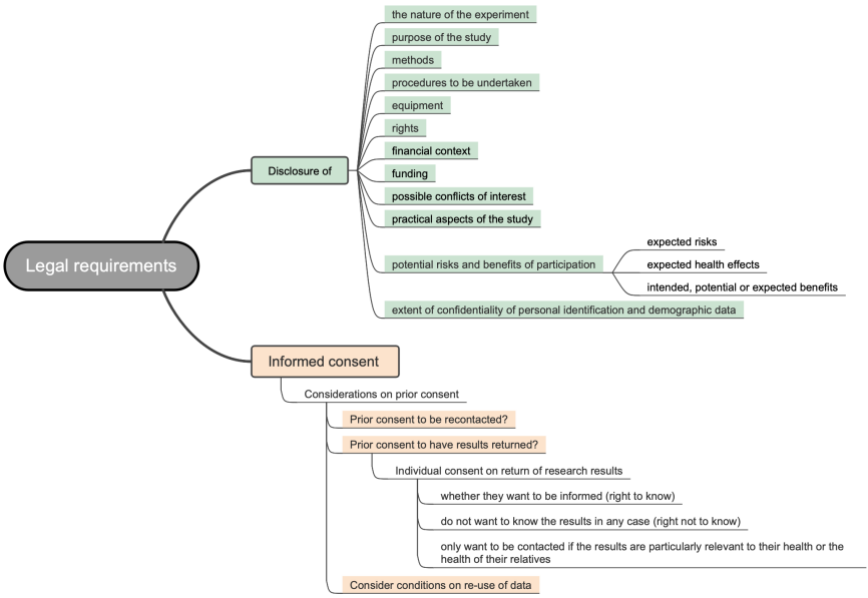


Figure 15: Overview of legal requirements regarding the disclosure of specific information related to the respective RbG study and how considering prior consent affects the disclosure and communication strategy.

Figure 13 provides a comprehensive overview of the legal obligations governing the disclosure of specific information within a genetic research study and the considerations for informed consent.

In the CHRIS study, the discussion between the researchers, the ELSI team, and the study coordinator ended with a consensus that for these RbG studies, the requirements for potentially recalling specific participants are that they consented to be recontacted and having results returned.

To enhance the informed consent process for RbG studies in biobanks, researchers could differentiate between information that

should be provided to fulfil the 'informing role' and information that must be fully 'understood' by participants, particularly concerning eligibility criteria and the implications of carrier status.

Dynamic consent models and multimedia tools offer promising avenues for facilitating tailored communication and disclosure strategies. Still, their accessibility and engagement need to be considered in the context of the study population. Participants have demonstrated appreciation for the ability to make informed choices, with some opting to change their preferences over time due to evolving life circumstances and opinions. Interestingly, most participants remembered which options they chose on the informed consent form regarding which typologies of research results they would want to have returned to (Kösters et al., 2019). However, not only in CHRIS but also in other study contexts, as reported by Haas et al. (2023), participants rarely changed their choices in dynamic consent platforms, raising questions about the investment into the development of such platforms. However, in CHRIS, despite a low rate of change at baseline, participants valued the opportunity to modify their informed consent decisions, which may have affected retention rates positively.

The CHRIS biobank's provision of three distinct options to participants acknowledges the vast array of attitudes and concerns that individuals may hold regarding the disclosure of genetic information. This approach closely aligns with the perspective proposed by Andorno (2004), who suggests that the right not to know should be explicitly activated through individual choice and

is not inherently absolute. This perspective acknowledges that disclosure might be deemed necessary under certain circumstances to avert serious harm to others. Furthermore, the biobank's inclusion of the option for participants to solely wish to be contacted if the disclosed results hold particular relevance to their health or that of their relatives is a commendable effort to preserve individual autonomy. The typologies allow participants to decide which genetic research results they want returned and clarify certain ethical considerations about the appropriateness of inviting the specific participant. This choice respects participants' autonomy over their genetic information and considers the interconnected nature of health within families and communities. However, on the other side, this highlights the importance of clarifying that researchers are not actively searching for genetic research results for the individual participant to avoid bespoken misunderstandings, as highlighted by Kösters et al. (2019).

In this context, another aspect that needs clarification is the potential lack of a broader societal conceptualisation of consent as an enabler and gatekeeper for ethical and societally accepted practices. Could, should or would families, or entire communities or cohorts, need ‘to decide’ together with a consensus or a democratic vote or a deliberate discussion on whether and how to participate in biobank studies or whether to have the carrier status disclosed?

Determining whether to reach a consensus on gene variant disclosure and research result return for all family members or to

accept divergent preferences and potential conflicts within the family is complex.

To address these challenges, scholars have raised the importance of a broader conceptualisation of reciprocity, involving researchers, individual participants, and society to decide whether individual consent is sufficient or whether some form of collective consent should be implemented (Fedeli, et al., 2019; Greely, 2001; Sanchini et al., 2016).

Moreover, considerations for understanding and supporting participants' autonomy in decision-making regarding disclosure necessitate the development of sensitively crafted and layered informed consent processes and informational materials, where the potential effects of the different frames have been considered.

Implications for Genetic Information Disclosure

This section initiates by exploring the factors that shape disclosure strategies, delving into considerations for nuanced approaches to disclosure, and addressing the balance between ethical obligations and participant preferences. Subsequently, we contextualise the findings from the CHRIS study within a broader framework and present ethical recommendations.

The scoping review shed light on various implications, dilemmas, and gaps, which necessitate the development of classification approaches and best practices for disclosing, returning and communicating research results, such as carrier status, to

participants. The identified differences in approaches to RbG studies and policies stem from underlying conflicting motivations regarding whether and how to disclose carrier status explicitly or implicitly to participants. In light of the absence of hard law regulations on issues such as disclosure in biobanks, soft law and other ethical recommendations have emerged to address some concerns regarding the ELSI of RbG studies. Consequently, addressing these issues requires technical and institutional solutions and ethical guidelines specific to each RbG study.

The design of strategies for disclosing genetic information to participants presents complex challenges, especially when the implications of specific genetic variants are uncertain. Nonetheless, the decision on whether and how to offer results must be addressed upfront by researchers, policymakers or other competent bodies because it is integral to the ethical conduct of the research (Beskow, 2017). To address them, researchers must consider contextual factors and conduct case-by-case assessments, considering risk assessment, clinical utility, and other contextual aspects, such as the study population. It would be impractical and ethically problematic to adopt a one-size-fits-all approach of either full disclosure or total nondisclosure of genetic information since full disclosure may raise concerns related to privacy, potential genetic discrimination, and the psychological impact, while nondisclosure may limit participants' right to make informed decisions about their health (Joly et al., 2014).

To approach the issue of disclosure in a nuanced and sensitive manner, it is first essential to define what form of disclosure will occur (partial, implicit, or explicit) and at what stage of the RbG study process (during prospective participant recall, during the RbG study, or after the study). Second, it is essential to consider whether this is consistent with the communicated initially and approved terms and conditions that the participants consented to and the biobank study expressed regarding their scopes and ways of working.

Contextual knowledge is crucial in decision-making regarding disclosing genetic results for all stakeholders. Researchers discussed arguments for and against a qualified disclosure policy during this discussion. Specific consideration should be given to cases where the knowledge of carrier status could skew the participants' perception and performance in the RbG study due to placebo effects or similar dynamics. For many RbG studies, the 'double-blind' study design must be retained during the study process because of voiced factors.

Furthermore, researchers considered factors such as risk assessment, clinical utility, and study population when determining the process and extent of disclosure. However, diverging views on defining categories and prioritising contextual factors can complicate decision-making. The scientific community lacks consensus on which results to return, who should be responsible for disclosure, and potential researcher liability. Recommendations for the return of results highlighted that the decision should be based on the

strength of association, phenotypic severity, clinical utility, and potential for improvement with treatment, following recommendations (Cassa et al., 2012; Vears et al., 2021).

In this discussion, we highlight that disclosing carrier status with uncertain clinical utility is a crucial matter that requires clarification. Few studies have explored the ELSI of uncertainty and ambiguities related to returned and returning results, such as carrier status, from WGS to participants of RbG studies.

Researchers in the CHRIS study context could not initially agree on how to respect people's preferences when they want to participate in follow-up studies but do not want the results to be returned. In previous consultations with ethics review boards and further discussions between the study coordinator and other researchers, the decision was taken that both conditions need to be fulfilled to invite participants, even though through the invitation and nondisclosure of the definitive carrier status, no 'real' return of research results occurs. From this case, the possibility of offering a choice to disclose the carrier status to the interested one after the study emerged. This choice provision could diminish concerns about partially disclosing the carrier status through the study objective in the invitation.

Expert involvement and reflexivity in decision-making are essential for balancing ethical obligations and participant preferences. Researchers highlighted the importance of reflexivity in deciding about contextual factors. They favoured the involvement of others trained in ethics and community engagement to inform decisions on

the appropriate disclosure policy. Likewise, the study personnel highlighted that experts should consider the potential personal or familial utility or benefit of returning the information on the carrier status after the specific RbG study.

A recent study by Kuiper et al. (2023) on ambivalence around best practices and norms in clinical genetic care suggests addressing issues through promoting explicit ethical collaboration, encouraging reflexivity, drawing diverse perspectives and disciplines to uncover and address ambivalence and enhancing informed and transparent genetic care practices.

Understanding the types of information that are important to participants and the appropriate phase of the study requires more than adherence to legal frameworks. Certainly, using "legal" regulations as a guiding principle may present some limitations in the context of research ethics. While legal regulations do play a crucial role in guiding the development of concrete frameworks, solely relying on legal mandates might inadvertently restrict the evolving landscape of research practices. The ethical, societal, and even scientific dimensions of research ethics extend beyond what legal frameworks can encompass. Furthermore, it's vital to differentiation between legal consent for data processing and ethical consent for participation in research studies and to clarify how legal grounds, like public or legitimate interest, might apply.

Currently, legal regulations do not cover or enforce some of the ethical principles that may be vital for participants in their process of participating in RbG research studies. Further research is needed

to investigate the importance of different ethical principles to participants in this context. Research on this is lacking and accordingly the worth of the different ethical for framework deserves more academic attention (Page, 2012). The discussion on sharing the carrier status with uncertain validity revealed different opinions among the researchers. Furthermore, the lack of time and economic resources for implementing processes to prevent these problems was acknowledged, as other studies have found (McGuire & Lupski, 2010; Purvis et al., 2020). Some parts of the recall procedures, the duty to recontact and the return of research results are specifically not regulated by laws and therefore ethical frameworks hold even more significance.

Research participants generally express a preference for receiving research findings and results consequently, we highlight the need to address this positive attitude towards the communication about carrier status that was identified in the CHRIS cohort and various other studies in this context (Beskow et al., 2011; Cadigan et al., 2011; Namey & Beskow, 2011; Tabor et al., 2011). Furthermore, discussions should be held for cases where genetic variants have uncertain consequences or implications for the participants because notwithstanding the lack of utility, participants might appreciate the possibility to receive such results (Vears et al., 2021).

In light of the overall positive results regarding the possibility of disclosing carrier status after the study, researchers should acknowledge the economic and practical implications for future RbG studies. Participants in the CHRIS study exhibited curiosity

about receiving information on their personal carrier status for various genetic variants, although their motivations and reasons varied. Furthermore, the empirical studies highlighted the participants interest to decide on whether to receive such findings after the study alongside genetic counselling or other expert guidance. As seen in another study by Nobile et al. (2017) participants wanted to learn about their own health status and this was a common motivation for enrolment and participation. To cater to diverse preferences and ensure inclusivity, communication and disclosure strategies for RbG studies should offer choices that avoid leaving anyone uninformed and respect specific preferences.

Additionally, particular attention should be given to the majority's increasing interest in receiving collective or aggregated results in a simplified manner while also providing the opportunity for participants to receive personal results after participating in a study. The approaches to disclosure and study-specific recall and communication strategies employed consent models and RoRR policies varied considerably. At the crux of this issue is the absence of clear standards defining the duty of the different involved key areas in the ethical responsibilities within research settings, where the duty to update or recontact participants remains ill-defined.

Defining the duty to re-contact, disclose and return research results, beyond the legal obligations, is a complex and multifaceted process, with varying perspectives and practices across different studies and jurisdictions. Further, these duties may change over time due to the evolving nature of the significance of genetic and genomic data

because the clinical significance or utility of carrier status information on certain genetic variants may change over time. While there is no general, established legal duty for physicians or other stakeholders as research institutes to affirmatively recontact former or current participants to update clinical advice based on newly discovered genetic information, there may be limited, specific situations where the responsible may have an ethical duty to provide updated genetic information, emphasizing the importance of solidarity, reciprocity, and co-production in study-participant relations.

In terms of the perceptions on the ethical duty to disclose results, there is a high heterogeneity in perspectives of participants and experts about ELSI of study specific RbG policies. However, participants' willingness to participate stems partially from their positive attitudes towards and gratitude for the disclosure of their genetic findings (Nurm et al., 2022). Accordingly, participants are informed beforehand through the information material about the type of variant and, in the course of consenting, some form of counselling could assist them in weighing up the pros and cons of receiving individual research results (Amendola et al., 2015; Mascalzoni et al., 2021; Papaz et al., 2019; Patch & Middleton, 2018; Thorogood et al., 2019).

A recent study by Nurm et al. (2022) compared the characteristics of people recalled for RbG studies on familial hypercholesterolemia with those of an unrecalled group with similar genetic profiles. It demonstrated that knowing one's carrier status affected outcomes

most. In accordance with another similar study by De et al. (2021)., low concerns from participants were related to the disclosure of genotype information, whereas the main concerns were related to the stress of participants or their family members. In this discussion about respecting preferences, the study personnel mentioned sensitivity (*feingefühl*) to finding balances and tailoring the communication approach to the context of the study and the people. Here, the importance of adequately providing study-related information was highlighted to support the decision-making process for participants, which was also observed in a similar study on the ethical aspects of genotype disclosure conducted by De et al. (2021). In the CHRIS context, the disclosure of the carrier status after an RbG study could occur through the study centre or other potential collaborators, such as general practitioners. This decision has economic and practical implications in terms of translating uncertain research results (either carrier status as the reason for eligibility or the results from the procedures and methods in the RbG study) into 'partially actionable or communicable' results and providing funding for other related aspects.

Effectively conveying the essential concepts of this RbG study, as penetrance and multifactorial disease etiologies for PD necessitate additional processes and the involvement of various experts. Furthermore, taxonomy serves as a valuable tool for all parties engaged in genomics, aiding them in comprehending and preparing for uncertainties in the field (Howard & Iwarsson, 2018). Ethicists,

clinicians, and policy experts contribute their perspectives, ensuring a comprehensive and ethically sound approach.

The disclosure and communication of information in an RbG study extend beyond conveying facts. This echoes a key concern among study personnel: effectively explaining the reasons for participant invitations without causing alarm. The delicate balance between informative clarity and overwhelming detail becomes evident during recall-invitation calls, underscoring the complexities in language use during this phase. They received calls clarifying some aspects for the participants, thus witnessing the difficulty of using 'adequate' language to inform prospective participants while not overwhelming them with too many details in the recall-invitation phase of the RbG study.

In conclusion, disclosing or communicating information about an RbG study to participants goes beyond mere conveyance of facts; it intricately involves framing various study details, notably its purpose and the eligibility criteria explored with this study. The potential to influence prospective participants' perceptions and willingness to participate through framing effects in the RbG study information material must be considered. Acknowledging the concerns mentioned earlier and using pragmatic criteria for disclosure may help address how informed consent is, to some extent, pre-emptive and used as an umbrella, as Chwang (2010) suggested.

Conversely, it is an ethical imperative to provide comprehensive and transparent information in the recall and informed consent process.

Collaborative approaches should be used to ensure accurate and unbiased information is given to participants. Feedback mechanisms should also be established to monitor participant satisfaction and comprehension of all stakeholders of the information materials and communication approach when designing and implementing research studies needing human participation.

Conclusion & Further Research

We have identified key issues and challenges associated with RbG approaches. In the CHRIS context, due to the aim and deliverables of this PhD project, we focused on ELSI around partial disclosure through study invitations and the lack of established best practices for disclosing information. Through comprehensive engagement with various stakeholders, including CHRIS participants, study personnel, coordinators, and researchers, we have identified challenges and refined the CHRIS RbG policy, information material and communication strategies for further RbG studies.

To effectively address the challenges related to the trajectory of recall, disclosure, and communication, we propose a participant-centric approach that empowers individuals to make informed decisions regarding the disclosure of their carrier status during the consent process. This allows participants to opt for receiving information about their carrier status post-study, promoting autonomy and ensuring transparency. The decision-making process regarding the return of research results is an essential ethical aspect that researchers and policymakers must proactively address. Returning research results to participants can be viewed as a gesture of appreciation for their time and effort in participating in the study, as was highlighted by study personnel and some researchers highlighting responsible resource stewardship and potential positive effects on the relationship between researchers and participants. Throughout our research stages, the significance of providing clear

and layered information, along with visual aids to enhance comprehension, has emerged as paramount. We recommend adopting a 'layered' approach to disclosure and communication, potentially through the dynamic consent model. This approach accommodates diverse participant preferences, enhances transparency for PDGR and facilitates informed decision-making.

To summarize the findings, considerations, and potential challenges encountered in extending the thesis recommendations beyond the CHRIS study we will conclude with a discussion on the broader applicability and significance of these adapted recommendations in fostering ethical practices in RbG studies across various contexts.

In the context of applying the recommendations developed for CHRIS to other research contexts, it's important to consider the specific characteristics of those contexts. For instance, in clinical settings with access to genotype data, the dynamic consent approach could be adapted to include specific provisions for RbG. This could involve additional layers of consent for the disclosure of genetic information, or specific communication strategies to ensure participants are fully informed about the implications. Considering the specific disease under study and the meanings attached to it (e.g., possible stigma or discrimination) and the socio-economic conditions (including the access to health care) where the study is conducted would allow a deepened reflection on the societal implications of RbG studies and the extent to which specific research practices are transferrable to other contexts. This implies a

limitation in the applicability of the present study's findings in different contexts.

Moving forward, further research is necessary to delve into the diverse reactions of participants based on their involvement in either healthy or patient populations. Additionally, exploring the impact of (partially) disclosed carrier status for different genetic variants on individuals, families, and communities is imperative. This insight is vital for crafting comprehensive guidelines and policies that promote responsible and equitable practices in the long run.

Likewise, understanding how different frames affect people's willingness to participate and the perception of value in the research study is also crucial. We suggest that further studies are conducted on framing effects and their influence on participants' comprehension and decisions. It is critical to identify which framing effects challenge the validity of consent and how they can be eliminated (Bhutta, 2004; Chwang, 2016).

Lastly, to strengthen future research in this field, we recommend involving diverse ELSI experts, as expanding investigations to other contexts will provide a deeper understanding of the ethical implications and societal considerations of RbG research, thereby leading to improved practices and outcomes. Ultimately, these efforts will contribute to the responsible advancement of RbG studies and the ethical stewardship of genetic information in research endeavours.

Strengths and Limitations

We tried to aim for a comprehensive, multi-step approach, incorporating various research methods and stages with stakeholders as critical voices in the research ecosystem, including participants, researchers, and study personnel. This inclusive approach ensured that the policy development process was well-informed by those with direct experience with RbG studies and their perspectives on ethical implications.

The embedded design allowed the study to elicit perspectives grounded in the experiences of individuals participating in RbG studies.

We encountered limitations to the study plan because of the COVID-19 pandemic, which disrupted and delayed the conduct of the RbG2 Study. For this study, originally, in-depth interviews were planned to be added to the quantitative survey, but because of precautions to limit the people in the study centre, the CHRIS study coordinators decided that interviews were not feasible; accordingly, we changed the methodology to a survey for the participants after the study participation.

For the surveys, we acknowledge that they are founded on a canon of interpretation and survey techniques, which rely on social and linguistic methods to ensure stability and ‘representativeness’ of the sample and that the stability condition required for survey analysis is not a natural property (Ashcroft, 2003).

As the study occurred within the context of the CHRIS study on specific genetic variants linked to PD, the generalisability of the findings may be limited to similar settings. The specific subpopulation of CHRIS participants who participated in an RbG study to study a specific PRKN variant might not be representative of the entire CHRIS cohort. Rather than insisting on perfect representativeness, we argue for the importance of considering the context of the research question and embracing the concept of saturation. We highlight the role of saturation, often used in qualitative research, allows for the purposive selection of participants until no new themes or perspectives emerge, providing a valid snapshot of relationships within the engagement sample (Murtagh et al., 2017). This approach offered possibilities to assess the comprehensiveness of the empirical studies and observations from the research context and proximity to the stakeholders.

The focus on carriers and nonmatched noncarriers of a specific genetic variant in the quantitative work introduced selection bias, potentially limiting the representativeness of the findings. Additionally, the inability to consider certain confounding variables, such as carrier status, during the analysis might have limited the interpretation of the results.

We could not recruit more ELSI experts with relevant experience in RbG studies for further FGDs due to time constraints, potentially limiting the depth of insight into the governance and oversight of biobanks in RbG research. Future research should consider including more diverse ELSI experts, such as research ethics

committee members, policymakers, and regulators, to provide a more comprehensive understanding.

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Appendix – Chapter 1

Detailed list of the included publications and the thematic and content analysis of the publications slightly adapted for the thesis (Year column was deleted due to space-issues).

Table 11: Overview of included publications in the final analysis of the scoping review.

Ref	title	type of document	journal	method & target sample	ethic*, legal*, social* or societal* terms found
(Beskow et al., 2004)	Ethical issues in identifying and recruiting participants for familial genetic research	Research Review	Am J Med Genet A	Literature review	- ethical issues, ethical concerns, ethical considerations, ethical principles, ethical barriers, ethical and scientific implications, ethically responsible research, ethically acceptable, ethical ramifications, ethical reason - societal benefits, societal value, social science research - no legal
(McGuire & McGuire, 2008)	Don't throw the baby out with the bathwater: enabling a bottom-up approach in genome-wide association studies	Editorial Material	Genome Res	Forum	- ethical considerations, centralized ethics review board - no societal, social - no legal
(Beskow et al., 2010)	Ethical challenges in genotype-driven research recruitment	Commentary	Genome Res	Case presentation	- ethical challenges, ethics consultation, research ethics consultation, basic ethical principles underlying the consent language, ethically appropriate disclosure, advice, and referral, ethical issues, ethical considerations of respect for persons, beneficence, paternalism, reciprocity, and the boundaries between research and clinical practice - no societal - no legal
(McGuire & Lupski, 2010)	Personal genome research : what should the participant be told?	Editorial Material	Trends Genet	Current practice and policy	- ethical challenges associated with whole genome sequencing (WGS) research is what to communicate to study participants?, ethical 'imperative' to return results in genetic research, ethical practical and scientific considerations, ethical commitment in research, - no societal but social science studies - legal guidance, moral or legal obligation to return results of unproven significance
(Beskow et al., 2011)	Research participants' perspectives on genotype-driven research recruitment	Journal Article	J Empir Res Hum Res Ethics	qualitative research, interviews with participants	- ethical challenges, ethically responsible research, ethically responsible research, interviewees' perspectives on ethical and policy issues, ethical issue, - ethical challenges stemming from the use and possible disclosure of genetic research results as part of the offer to participate in additional research
(Cadigan et al., 2011)	The meaning of genetic research results: reflections from individuals with and without a known genetic disorder	Journal Article	J Empir Res Hum Res Ethics	qualitative research, in-depth interviews	- researchers and ethics boards, - ethical, legal, and social implications
(Namey & Beskow, 2011)	Epilepsy patient-participants and genetic research results as "answers"	Journal Article	J Empir Res Hum Res Ethics	qualitative research, semi-structured interviews	- ethical challenges, ethical dilemmas surrounding the complex and muchdebated issue of return of individual genetic research results, - no societal - no legal
(Tabor et al., 2011)	Parent perspectives on pediatric genetic research and implications for genotype-driven research recruitment	Journal Article	J Empir Res Hum Res Ethics	qualitative research, interviews with parents of epilepsy patient-participants	- ethical considerations about the use and disclosure of genetic information as part of the recruitment process, ethical challenges in pediatric genetic research studies that intersect with ethical issues involving genotype-driven research recruitment, - no societal - no legal
(Beskow, 2012)	IRB chairs' perspectives on genotype-driven research recruitment	Journal Article	IRB Ethics and Human Research	Qualitative research, Survey with commercial and institutional IRBs	- ethical challenges, ethically acceptable approaches to genotype-driven recruitment depending on context, - ethical Dilemmas: Weighing the Issues, (ethical concerns shifted to the recruitment phase when genetic information that is generated in one study is used as the basis for identifying and recontacting participants about further research) - no societal - no legal
(Beskow et al., 2012)	Recommendations for ethical approaches to genotype-driven research recruitment	Journal Article	Human genetics	Workshop with wide range of stakeholders	- ethical challenges, ethical issues associated with recontacting participants for the purpose of additional research recruitment and with genotype-driven recruitment, - no societal - no legal
(Michie et al., 2012)	Am I a control?: Genotype-driven research recruitment and self-understandings of study participants.	Original research article	Genetics in medicine : official journal of the American College of Medical Genetics	Qualitative research, Multisite study, workshop with multiple stakeholders	- recommendations for ethical approaches to genotype-driven research recruitment, - no societal - no legal

(Oliver et al., 2012)	Balancing the risks and benefits of genomic data sharing: genome research participants' perspectives	Original paper	Public Health Genomics	randomized trial of three consent types, follow-up interviews	- advance the ethical conduct of genome research, general societal benefits of participating in research - ELSI
(Budin-Ljosne et al., 2013)	Genotype-driven recruitment: a strategy whose time has come?	Journal Article	BMC Med Genomics	Debate	- ethical issues, ethical concerns - societal implications of recruiting individuals in original GDR studies - questions related to the legal authority of these committees may emerge, legal framework
(Olson et al., 2014)	Biobanks and personalized medicine	Review	Clin Genet,	Mini-review	ethical concerns - no societal - no legal
(Atabaki-Pasdar et al., 2016)	Statistical power considerations in genotype-based recall randomized controlled trials	Journal Article	Scientific reports	Article, Comparative study	specific ethical considerations for GBR trials - no societal - no legal
(Beskow, 2017)	Genotype-Driven Recruitment and the Disclosure of Individual Research Results	Editorial Material	Am J Bioeth	Editorial Material	- several ethically acceptable approaches to genotype-driven recruitment depending on context - plans for minimizing risks and managing ethically appropriate disclosure, advice, and referral - no societal - no legal
(Doernberg & Hull, 2017)	Harms of Deception in FMR1 Premutation Genotype-Driven Recruitment	Editorial Material	Am J Bioeth	Editorial Material	- ethical questions about the nature of the study - ethical duties to disclose results - no societal - no legal
(Ossorio & Mailick, 2017)	Genotype-Driven Recruitment Without Deception	Editorial Material	Am J Bioeth	Case commentaries	- ethical challenges for genotype-driven research - no societal - no legal
(Taylor et al., 2017)	Genotype-Driven Recruitment in Population-Based Biomedical Research	Case report	Am J Bioeth	Case report	- ethical and research design reasons - ethical concerns regarding the disclosure of research results in the context of genotype-driven recruitment - ethical consent process - no societal - no legal
(Khera & Kathiresan, 2017)	Genetics of coronary artery disease: discovery, biology and clinical translation	Review	Nature Reviews Genetics	Review	- alteration of an individual's DNA raises a host of ethical and social questions - no societal - no legal
(Corbin et al., 2018)	Formalising recall by genotype as an efficient approach to detailed phenotyping and causal inference	Review	Nat Commun	Review and comparative study	- ethical challenges associated with recruitment by genotype - specific ethical issues - ethical principles of respect and reciprocity - ethical balance for RbG studies - no societal - no legal
(Franks & Timpson, 2018)	Genotype-Based Recall Studies in Complex Cardiometabolic Traits	Review	Circ Genom Precis Med	Review	- ethical barriers - no societal - no legal
(Minion et al., 2018)	The ethics conundrum in Recall by Genotype (RbG) research: Perspectives from birth cohort participants	Research Article	PloS one	qualitative research, semi-structured interviews with participants	novel ethical context and challenges, ethical principle of autonomy, basis of informed consent in contemporary researchis pitched against the 'right not to know', non-maleficence (the precept to do no harm) - participants demonstrated societal solidarity - ethical, legal or other normative principles
(Momozawa & Mizukami, 2021)	Unique roles of rare variants in the genetics of complex diseases in humans	Review	Journal of Human Genetics	Review	- ethical, social, and legal implications of population screenings conducted mainly in specific high-risk populations,
(Finer et al., 2020)	Cohort Profile: East London Genes & Health (ELGH), a community-based population genomics and health study in British Bangladeshi and British Pakistani people	Article	Int J Epidemiol	Cohort profile	- subject to ethics approval - societal: overrepresentation of specific populations and underrepresentation of others

Appendix – Chapter 2

The Appendix for chapter two includes supplementary materials in the form of Information material, Questionnaires and the semi-structured translated interview guide (From german to English).

Information material

Vertiefende neurologische Untersuchung

Information für Studienteilnehmende PAREGEN

1. Einführung

Worum handelt es sich in vorliegendem Forschungsprojekt?

In den letzten Jahren hat sich gezeigt, dass sich im Rahmen von neurogenetischen Erkrankungen der Zusammenhang zwischen Genotyp und Phänotyp komplexer darstellt als zuvor vermutet: es konnten zahlreiche Träger von vermeintlich krankheitsverursachenden Mutationen identifiziert werden, die keine Zeichen der Erkrankung aufweisen. Viele Menschen tragen solche Varianten. Entweder sind die Symptome bei diesen Menschen sehr schwach oder sie weisen bestimmte Faktoren auf, die sie vor möglichen Krankheiten schützen. Dieses Phänomen wird als reduzierte Penetranz bezeichnet. Das Ziel dieser Studie ist es, Mechanismen zu untersuchen, die vor Krankheiten schützen können, mit einem besonderen Fokus auf Varianten im Parkin-Gen.

Varianten in diesem Gen können bei Auftreten von zwei Mutationen (homozygot) eine genetische Parkinson-Krankheit verursachen, und es gibt Hinweise darauf, dass das Tragen einer einzelnen Mutation (heterozygoter Zustand) das Risiko für das Auftreten einiger abgeschwächter klinischer Symptome erhöhen kann.

Wo wird die Studie durchgeführt und wer wird um eine Teilnahme gefragt?

Diese Studie ist eine Folgestudie der CHRIS-Studie, eine vom Institut für Biomedizin (Eurac Research) und den Südtiroler Gesundheitsbetrieben durchgeführte longitudinale Studie, zu der die erwachsene Bevölkerung aus dem Vinschgau in Südtirol systematisch eingeladen wird. Die Studie wird somit am CHRIS-Studienzentrum im Krankenhaus Schlanders durchgeführt.

CHRIS-Studienteilnehmende sind grundsätzlich gesunde Teilnehmende an einer Bevölkerungsstudie und weitere phänotypische Informationen werden benötigt, um die Informationen von genetischen Daten besser interpretieren zu können. Es werden anhand von Genotypen im Parkin-Gen ausgewählte Probanden eingeladen: genotypisch unauffällige Probanden und Probanden mit einer einzelnen heterozygoten Variante im Parkin-Gen. Die Gruppenzugehörigkeit wird nicht mitgeteilt, da damit keine unmittelbaren individuellen

Konsequenzen verbunden sind. Unsere Forschungen zielen darauf ab, schützende Faktoren zu identifizieren, im Moment haben wir aber noch keine Ergebnisse, aus denen sich ein klinischer Nutzen für Sie ergeben könnte.
Siehe auch online: de.chris.eurac.edu/paregen

2. Untersuchungsprogramm

Das Untersuchungsprogramm umfasst folgende Teile:

- Klinisch-neurologische Untersuchung (MDS-UPDRS III und IV, inkl. Videoaufzeichnung)
- Durchführung einer transkraniellen Sonografie (Ultraschalluntersuchung des Gehirns)
- Erhebung eines PD-spezifischen Minimal-Datensatzes (MDS-UPDRS I und II)
- Schriftprobe und Spiralenzeichnen
- Ganganalyse mit dem Mobility Lab
- Geruchtstest
- Einfache Blutprobe (für die Anlegung von Zellmodellen)
- Befragung zu persönlichen Eindrücken und Empfinden bezüglich der Studie/Untersuchung

Die Untersuchungen werden von qualifiziertem und spezifisch geschultem Personal im Krankenhaus Schlanders durchgeführt.

Erhalte ich die Ergebnisse der Untersuchung?

Die Befunde der klinischen Untersuchung werden Ihnen gleich nach der Untersuchung mitgeteilt, sofern für Ihre Gesundheit relevante Ergebnisse auftreten sollten.

Welche Art von Forschung wird durchgeführt und welche Rolle spielt dabei meine DNA und meine genetischen Daten?

Die Analyse der Erbsubstanz der CHRIS-Studienteilnehmende, die im Rahmen der CHRIS Studie durchgeführt wurde, hat zur Identifizierung von Probanden mit einzelnen heterozygoten Genvarianten im Parkin-Gen geführt. In dieser Studie möchten wir besser verstehen, welche Bedeutung diese heterozygoten Varianten für die Gesundheit haben und Faktoren identifizieren, die vor Krankheiten schützen können. Dazu ist eine standardisierte neurologische Untersuchung, ein transkranieller Ultraschall sowie die Beurteilung durch einen erfahrenen Neurologen vorgesehen.

Erhalte ich die Ergebnisse dieser Analysen?

Diese Studie dient ausschließlich dazu, das medizinisch-genetische Wissen über die untersuchte Krankheit zu verbessern. Wir informieren Sie, dass Ihre Blutprobe infolge der genetischen Informationen nicht nur über Ihre Gesundheit, sondern auch über die Ihrer Familienmitglieder Aufschluss geben könnte. Die Studie wird aber ausschließlich zu Forschungszwecken durchgeführt. Die

Ergebnisse werden Ihnen nicht mitgeteilt, da sie für eine persönliche genetische Beratung nicht geeignet sind. Die Ergebnisse werden in anonymisierter Form wissenschaftlich ausgewertet.

Gibt es Risiken?

In dieser Studie werden nur Untersuchungen durchgeführt, die mit keinerlei Risiko für Ihre Gesundheit verbunden sind. Nach der Blutentnahme kann es in seltenen Fällen zu einem kleinen Hämatom (Bluterguss) an der Entnahmestelle kommen.

Aufklärung und Freiwilligkeit

Die Studienteilnahme ist freiwillig. Die Studienteilnehmende werden Ihr schriftliches Einverständnis zur Teilnahme geben, nachdem sie die Studienteilnehmenden ausführlich gelesen und verstanden hat. Die Einverständniserklärung kann jeder Zeit widerrufen werden. Der Widerruf geschieht durch eine schriftliche oder telefonische Mitteilung an den Verantwortlichen der Datenverarbeitung und bringt keinerlei Nachteile für die Teilnehmende mit sich.

3. Aufbewahrung von biologischem Material und Durchführung der Studie

Wie bei der CHRIS Studie werden aus ihrer Blutprobe Zellen extrahiert und in Kultur gebracht. Diese Zelllinien (immortalisierte Blutzellen und induzierte pluripotente Stammzellen, die zu Neuronen differenziert werden können) werden mit Hilfe einer Zahlencodierung codifiziert und in der Biobank des Instituts für Biomedizin an der Eurac Research in Bozen für den Zeitraum von 30 Jahren aufbewahrt und für Forschungsvorhaben verwendet.

4. Finanzierung der Studie

Die Kosten dieser Studie trägt das Institut für Biomedizin der Eurac Research, finanziert von der Autonomen Provinz Bozen - Südtirol, Abteilung Bildungsförderung, Universität und wissenschaftliche Forschung. Darüber hinaus wird diese Studie von der Deutschen Forschungsgemeinschaft (DFG): Forschergruppe FOR 2488 (Prof. Dr. Christine Klein, Universität Lübeck, Deutschland) für das Projekt "Reduced penetrance in hereditary movement disorders: Elucidating mechanisms of endogenous disease protection" gefördert.

5. Datenschutz und Möglichkeit zu Folgestudien

Wie ist die Einhaltung der Datenschutzbestimmungen und der Privacy gesichert?

Im Sinne des Gesetzesdekret n. 196/03 bezüglich des Schutzes von Personen bei der Verwendung persönlicher Daten sowie im Sinne der VERORDNUNG (EU) 2016/679 DES EUROPÄISCHEN PARLAMENTS UND DES RATES informieren wir Sie, dass Ihre persönlichen Daten entsprechend der Datenschutzbestimmungen gesammelt und aufbewahrt und ausschließlich zu Forschungszwecken verwendet werden. Sie haben bei Ihrer ersten Teilnahme an der CHRIS-Studie entschieden, wie Ihre Daten behandelt werden sollen. Ihre Zustimmung ist noch gültig und Sie können sie im persönlichen Bereich „MY CHRIS“ auf der Internetseite jederzeit widerrufen oder abändern. Wie in der CHRIS Studie, werden auch in dieser Folgestudie Ihre medizinischen Daten und das biologische Material mit Hilfe einer Zahlencodierung pseudonymisiert und getrennt von den persönlichen Daten, wie z.B. Name und Adresse, aufbewahrt. Die Zuordnung ihrer persönlichen Daten zu den Forschungsergebnissen ist dann nur noch dem Studienleiter und den von ihm beauftragten Mitarbeitern möglich. Gesammelte Informationen werden als streng vertraulich betrachtet und unterliegen dem Berufsgeheimnis. Die Daten und das biologische Material werden eventuell nur in anonymisierten Form mit den Forschungspartnern ausgetauscht. Die Daten werden in anonymisierter Form in Fachzeitschriften veröffentlicht oder auf Tagungen vorgestellt. Falls Sie es wünschen, haben Sie das Recht zu erfahren, welche und wie die Informationen aufbewahrt werden.

6. Ergebnisse der Studie

Für die Studienteilnahme ist keine Art von Vergütung vorgesehen. Langfristig ist zu erwarten, dass sich durch die Kenntnis genetischer Einflüsse auf die untersuchte Erkrankung Vorteile für die Gesundheit der Bevölkerung ergeben. Ein eventueller Gewinn aus dieser Studie wird ausschließlich für die Finanzierung weiterer biomedizinischer Forschungsprojekte in Südtirol verwendet werden.

7. Rechte des Studienteilnehmenden

Die Rechte der Studienteilnehmenden bezüglich der Ihnen betreffenden Daten sind in der Einverständniserklärung zur CHRIS-Studie wie folgt beschrieben:

1. Die betroffene Person hat das Recht, Auskunft darüber zu erhalten, ob Daten vorhanden sind, die sie betreffen, auch dann, wenn diese noch nicht gespeichert sind; sie hat ferner das Recht, dass ihr diese Daten in verständlicher Form übermittelt werden.
2. Die betroffene Person hat das Recht auf Auskunft über
   a) Die Herkunft der personenbezogenen Daten;
   b) Den Zweck und die Modalitäten der Verarbeitung;
   c) Das angewandte System, falls die Daten elektronisch verarbeitet werden;
   d) Die wichtigsten Daten zur Identifizierung des Rechtsinhabers, der Verantwortlichen und des im Sinne von Artikel 5 Absatz 2 namhaft gemachten Vertreters;
   e) Die Personen oder Kategorien von Personen, denen die personenbezogenen Daten übermittelt werden können oder die als im Staatsgebiet namhaft gemachten

Vertreter, als Verantwortliche oder als Beauftragte davon Kenntnis erlangen können.

3. Die betroffene Person hat das Recht,
   a) Die Aktualisierung, die Berichtigung oder, sofern interessiert, die Ergänzung der Daten zu verlangen;
   b) Zu verlangen, dass widerrechtlich verarbeitete Daten gelöscht, anonymisiert oder gesperrt werden; dies gilt auch für Daten, deren Aufbewahrung für die Zwecke, für die sie erhoben oder später verarbeitet wurden, nicht erforderlich ist;
   c) Eine Bestätigung darüber zu erhalten, dass die unter den Buchstaben a) und b) angegebenen Vorgänge, auch was ihren Inhalt betrifft, jenen mitgeteilt wurden, denen die Daten übermittelt oder bei denen sie verbreitet wurden, sofern sich dies nicht als unmöglich erweist oder der Aufwand an Mitteln im Verhältnis zum geschützten Recht unvertretbar groß wäre.

8. Rechtsinhaber und Verantwortlicher der Datenverarbeitung

Eurac Research mit Sitz in Bozen, in Person des gesetzlichen Vertreters Prof. Roland Psenner, ist „Rechtsinhaber der Datenverarbeitung“. Um weitere Informationen zu erhalten, können Sie das CHRIS Studienzentrum kontaktieren. Das Ihnen vorgestellte Studienprotokoll wurde vom Ethikkomitee des Südtiroler Sanitätsbetriebs genehmigt.

Questionnaires

The first questionnaire, which focused on the emotions at the time of invitation and satisfaction with the information received, was submitted before the clinical examination. The interview covered reasons for participation, response to invitation and assessment of the information provided, views, preferences, and concerns on disclosures, return of research results, and participation in future RbG studies. After the interview, participants answered the second questionnaire, which was focused on both the current RbG experience (emotions and concerns related to the disclosed information, preferences for disclosure of carrier status and return of individual genetic research results, satisfaction with the provided information) and preferences for recruitment and disclosure in further hypothetical studies (interest in further participation, evaluation of RbG research practices, preferences for disclosure of disease under study). The double assessment of emotions was meant to capture possible changes following participation. The questionnaires and the interview guide were informed by the insights obtained from a previously conducted qualitative study on the return of research results (Kösters et al., 2019). The questionnaires and the interview guide are reported below.

Questionnaire 1 – Before participating

Sehr geehrte/r TeilnehmerIn an der vertiefenden neurologischen Untersuchung PAREGEN,
Danke, dass Sie heute an unserer Studie teilnehmen!
Bevor Sie mit den Untersuchungen beginnen, möchten wir wissen, wie Sie sich beim Erhalt der Einladung gefühlt haben. Alle Daten werden vertraulich behandelt und dienen der Verbesserung unseres Kommunikationsprozesses.

Wie haben Sie sich gefühlt, also Sie die Einladung für die heutige Studie erhalten haben?
Bitte wählen Sie einen Wert zwischen 1 (habe ich nicht verspürt) und 5 (habe ich stark verspürt) für jede der genannten Emotionen.
Als ich die Einladung erhalten habe, fühlte ich mich…

	1	2	3	4	5
… neugierig	☐	☐	☐	☐	☐
… ängstlich	☐	☐	☐	☐	☐
… besorgt	☐	☐	☐	☐	☐
… erfreut	☐	☐	☐	☐	☐
… verärgert	☐	☐	☐	☐	☐
… sorglos	☐	☐	☐	☐	☐
…erleichtert	☐	☐	☐	☐	☐
… nervös	☐	☐	☐	☐	☐

Andere:

_____

Warum haben Sie sich so gefühlt? Bitte beschrieben Sie kurz Ihre persönlichen Überlegungen.

Wurden durch die Informationsmaterialien, die Sie vor Ihrer Teilnahme erhalten haben, Ihre Fragen zur Studie ausreichend beantwortet?

- ☐ Nein, viele nicht.
- ☐ Nein, einige nicht.
- ☐ Ja, die meisten.
- ☐ Ja, alle.

Vielen Dank für Ihr Feedback.

Questionnaire 2 – after the RbG study examination

Sehr geehrte/r TeilnehmerIn an der vertiefenden neurologischen Untersuchung PAREGEN,
Ihre Meinung zur heutigen Studie ist uns wichtig!
Durch diesen Fragebogen möchten wir Ihre Bewertung der Studie und der erhaltenen Informationen erfassen. Alle Daten werden vertraulich behandelt und dienen der Verbesserung unseres Kommunikationsprozesses.

1. Wie fühlen Sie sich, nachdem Sie an der Studie teilgenommen haben?
   Bitte wählen Sie einen Wert zwischen 1 (habe ich nicht verspürt) und 5 (habe ich stark verspürt) für jede der genannten Emotionen.

Nachdem ich an der Studie teilgenommen habe, fühle ich mich…

	1	2	3	4	5
… neugierig	☐	☐	☐	☐	☐
… ängstlich	☐	☐	☐	☐	☐
… besorgt	☐	☐	☐	☐	☐
… erfreut	☐	☐	☐	☐	☐
… verärgert	☐	☐	☐	☐	☐
… sorglos	☐	☐	☐	☐	☐
…erleichtert	☐	☐	☐	☐	☐
… nervös	☐	☐	☐	☐	☐

Andere:

_____

Warum fühlen Sie sich so? Bitte beschrieben Sie kurz Ihre persönlichen Überlegungen.

---

2. Haben Sie darüber nachgedacht, ob Sie die Genvariante haben, die mit der Parkinsonkrankheit in Verbindung steht, als Sie die Einladung für die heutige Studie erhalten haben?

   ☐ Ja ☐ Nein

3. Bereitet es Ihnen Sorgen, dass Sie Träger der Genmutation im Parkin-Gen sein könnten?

Große Sorgen	Einige Sorgen	Wenige Sorgen	Gar keine Sorgen	Ich weiß nicht
☐	☐	☐	☐	☐

4. Wie schätzen Sie Ihr Risiko ein, selbst irgendwann an Parkinson zu erkranken?

Sehr hohes Risiko	Erhöhtes Risiko	Niedriges Risiko	Kein Risiko	Ich weiß nicht
☐	☐	☐	☐	☐

5. Bitte geben Sie an, inwieweit Sie folgenden Aussagen zustimmen:

   a) Ich schätze mein Risiko Parkinson zu entwickeln heute höher ein, als bevor ich zu dieser Studie eingeladen wurde.

Stimme nicht zu	Stimme eher nicht zu	Weder noch	Stimme eher zu	Stimme zu
☐	☐	☐	☐	☐

b) Ich mache mir heute mehr Sorgen darüber einmal selbst Parkinson zu entwickeln, als bevor ich zu dieser Studie eingeladen wurde.

Stimme nicht zu	Stimme eher nicht zu	Weder noch	Stimme eher zu	Stimme zu
☐	☐	☐	☐	☐

6. Hätten Sie gerne gewusst, ob Sie Träger der Genmutation sind oder zur Kontrollgruppe ohne Genmutation gehören?

☐ Ja ☐ Nein

7. Für wie wahrscheinlich halten Sie es, dass Sie zur Kontrollgruppe gehören, die keine Mutation im Parkin-Gen aufweist?

Sehr wahrscheinlich	Eher wahrscheinlich	Weder noch	Eher unwahrscheinlich	Sehr unwahrscheinlich
☐	☐	☐	☐	☐

8. Haben Sie Verwandte, die an Parkinson erkrankt sind?

☐ Ja ☐ Nein

9. Im Rahmen dieser Studie werden Sie die klinischen Befunde Ihrer neurologischen Untersuchung erhalten, sofern diese für Ihre Gesundheit relevant sind. Es ist jedoch nicht vorgesehen,

dass Sie genetische Forschungsergebnisse aus dieser Studie erhalten - weder individuelle noch allgemeine. Wie finden Sie das?

☐ Das ist für mich in Ordnung. ☐ Das finde ich schade.

☐ Das ist mir gleichgültig.

10. Wurden durch die Informationen und Beratung, die Sie vor Ort erhalten haben, all Ihre Fragen beantwortet?

☐ Nein, viele nicht.

☐ Nein, einige nicht.

☐ Ja, die meisten.

☐ Ja, alle.

11. Konnten mögliche Fragen oder Zweifel, während Ihrer Teilnahme ausreichend beantwortet oder aufgeklärt werden?

☐ Ja ☐ Nein

Falls Nein: Welche Fragen konnten nicht beantwortet werden? Warum konnten Sie nicht beantwortet werden?

_____

12. In der Zukunft planen wir weitere Studien dieser Art durchzuführen.
    a) Möchten Sie an ähnlichen Studien teilnehmen?

☐ Ja ☐ Nein

Falls Nein: Welche Voraussetzungen müssten erfüllt sein, damit Sie erneut teilnehmen würden?

_____

b) Hätten Sie es vorgezogen, wir hätte Sie zu der heutigen Studie nicht eingeladen?

☐ Ja ☐ Nein

Falls Ja: Warum? Bitte schildern Sie kurz Ihre persönlichen Beweggründe.

_____

13. Einige andere Forschungsinstitute teilen ihren Studienteilnehmern nicht mit, mit welcher genetischen Krankheit die untersuchte Genvariation, im Zusammenhang steht. Sie sprechen bei der Einladung zu Folgestudien lediglich von „weiterer genetischer Forschung".
    a) Wie bewerten Sie dieses Vorgehen?

Sehr negativ	Eher negativ	Teils/Teils	Eher positiv	Sehr positiv
☐	☐	☐	☐	☐

b) Würden Sie wissen wollen, mit welcher Krankheit die untersuchte Genvariation im Zusammenhang steht, wenn Sie zu einer weiteren Studie eingeladen werden?

☐ Ja ☐ Nein ☐ Das ist mir unwichtig.

c) Genmutationen können mit den verschiedensten Krankheiten in Verbindung stehen. Dies können Krankheiten sein, die durch ihre milde Symptomatik das

alltägliche Leben nur geringfügig beeinflussen. Jedoch können auch schwere Krankheiten, für die es keine Heilung gibt, genetisch bedingt sein.
Würde die Art der Krankheit Ihre Entscheidung, ob Sie wissen möchten um welche Krankheit es sich handelt, beeinflussen?

☐ Ja ☐ Nein

Vielen Dank für Ihr Feedback.

Interview guide (translated)

Expectations

- Why are you participating in today's study?
- What were your expectations?

Response to invitation

- Did you understand why you were selected to participate in this study?
- What did you think when you received the invitation?
- Did you think about your health?
- How did these thoughts make you feel? / How did you feel?

Communication Parkin gene variant

- Did you think about whether you have the gene variant associated with Parkinson's disease?
- Would you like to know which group you belong to? Why?
- What feelings does the thought that you might have the gene variant trigger in you?
- How do you estimate your risk of developing Parkinson's disease at some point?
- Do you assess your risk differently today than before participating in this study?
- Are you concerned that you may carry the gene variant? Why?

- If you had not been invited to participate in this study, you probably would not have thought about it:
- Would you have preferred not to have been invited?

Results

- You are not expected to receive research results from this study - neither individual nor general:
- What do you think about it?

Communication

- We would also like to know how you rate this study's communication.
- Did the information you received before participation leave any doubts or questions you would have liked to have clarified before the study?
- Are there any doubts or questions you would like to ask now?
- Do you think a follow-up is necessary or desirable?

Further studies

- In the future, we plan to conduct further studies of this kind.
- Would you participate in other similar studies? Why?
- Would you have preferred not to be invited to this study?
- Some similar studies do not tell their participants which disease the genetic variant being studied is associated with.

What do you think about this? Would this be a good solution?

- Would you like to know to which disease the genetic variation being studied is related? Why/why not?
- Do you think it makes a difference which disease it is? (fatal disease vs. mild disease)

Appendix – Chapter 3

The Appendix for Chapter 3 includes the information material about RbG that was designed in collaboration with the EURAC Communication Teams, ELSI Team and the CHRIS study coordinators. Further, the survey structure and questions are attached in one of the orginal languages of the survey.

Focus group discussion – semistructured interview guide

Focus Group Discussion with Researchers

The focus group discussion protocol is structured as follows:

- Welcome participants
- Short presentation of the research team and the significance of the contribution expected from participants for the project
- Short presentation of the researchers and their work, role

We used a presentation to accompany the discussion with a slide for each different theme of the FGD:

1. Warming up: Participants are asked to choose a cartoon and relate it to themselves.
2. Participants are asked to discuss the factors that are most relevant when designing a Recall-by-genotype (RbG) study, using a link provided to write their answers. The aim is to obtain researchers' perspectives on the decisive factors that shape RbG study design.

3. Participants are asked to discuss the reasonings behind choosing the adequate sampling and recruitment strategy.
4. Participants are asked to discuss the issue of implicit or explicit disclosure through the study invitation to an RbG study, which contains genetic information.
5. Participants are asked to consider the ELSI challenges related to RbG studies.
6. Specific ELSI challenges identified by the CHRIS study are presented.

Participants are presented with results from the Pilot study that confirmed that, and the participants want to know with which disease the investigated genetic variation is associated with BUT when asking if the type of disease influences the decision about participation, the results are split and people have different opinions on why and when they want to know and when not.

a. How do you account for the preferences of participants if they are split?
b. What rules should be used to decide on disclosing the carrier status or not?
c. Present results from participants feedback and discuss implications
d. How should researchers invite participants and family members while preventing the “is there

something wrong with me/our family?" concerns of participants?

7. All things considered questions: Hypothesizing possible scenarios for future RbG studies?
8. Final remarks? Have we missed anything?

Focus Group Discussion with the study personnel

We used a presentation to accompany the discussion with a slide for each different theme of the FGD:

1. Warming up: Present a picture to the participants and a question, for example: "We are here today to discuss a Recall by Genotype CHRIS follow-up study. What do you think this means?" Encourage participants to share their thoughts and ideas.
2. Material to Explain Terminology and Study Design Explain the following terms to participants:

Use visual aids and stimulus material to explain the concept of RbG in the CHRIS cohort. Ask participants about the differences between such RbG studies as PAREGEN and other follow-up studies. Discuss ethical, legal, and social issues (ELSI) with examples:

4. Stimulus Material: Ethical, Legal, and Social Challenges (ELSI) Present the following ELSI challenges to participants, along with examples.

- Violation of the person's right not to know.
- Participants may receive results of screenings with uncertain clinical significance.
- Participants may not understand why they are invited to participate in the RbG study.

- Emotional distress for participants and their families, including anxiety and burdens.
- No results as motivation or compensation.
- Duration and complexity of study examinations.
- Complexity of study questions that may be difficult for participants to understand.
- Potential confrontation of family members with genetic information if the implications of the study's specific variant are relevant to them.

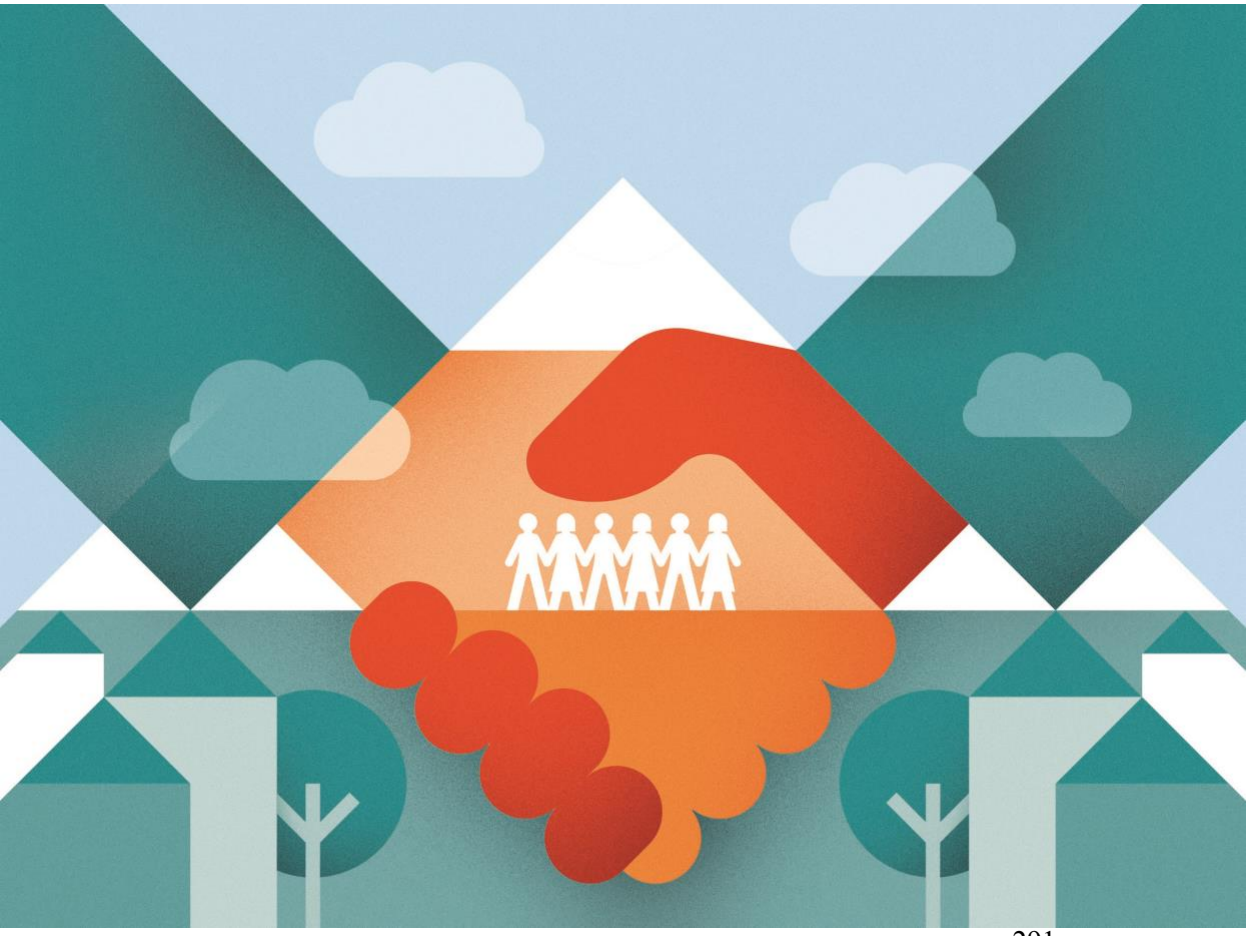
5. Participants are asked to consider the ELSI challenges related to RbG studies.
6. Questions about specific ELSI challenges identified by them in the process of the RbG study
7. All things considered, questions: Hypothesizing possible scenarios for future RbG studies?
8. Final remarks? Have we missed anything?

Information material

CHRIS
eurac research

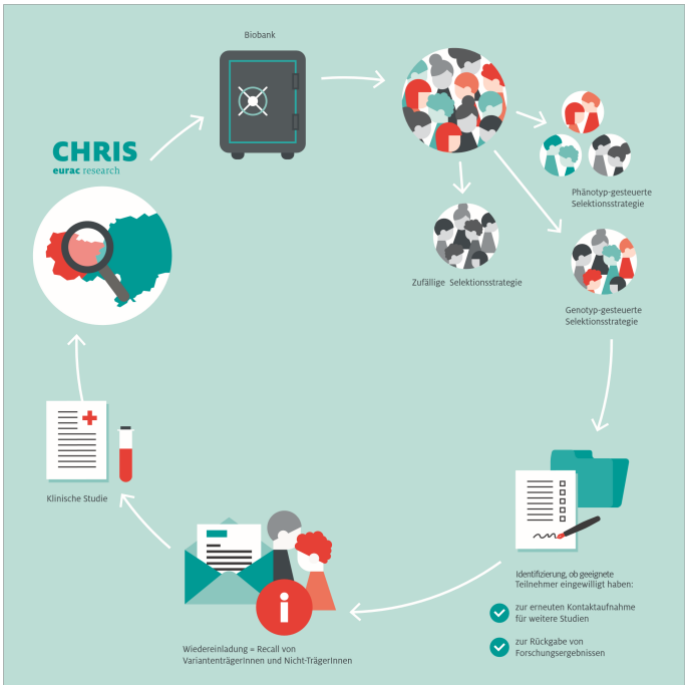
AUTONOME PROVINZ BOZEN – SÜDTIROL
PROVINCIA AUTONOMA DI BOLZANO – ALTO ADIGE
PROVINZIA AUTONOMA DE BULSAN – SUDTIROL
Südtiroler Sanitätsbetrieb
Azienda Sanitaria dell'Alto Adige
Azienda Sanitera de Sudtirol

Recall-by-Genotype (RbG) Studien



Was sind Recall-by-Genotype (RbG) Studien?

Recall by Genotype (RbG) ist ein Forschungsdesign, bei dem Forschungsteilnehmende auf der Grundlage ihres Genotyps (siehe erklärende Grafik) ausgesucht und eingeladen werden. Bei diesem Ansatz nutzt die Wissenschaft bestehende Daten von Teilnehmenden aus Studienpopulationen, für die Genotyp- oder vollständige Sequenzdaten verfügbar sind, um Träger:Innen einer Variante und Nicht- Träger:Innen (Menschen ohne diese Variante) einer bestimmten Genvariante zu identifizieren. Die Teilnehmenden (Variantenträgern:Innen und Nicht-Träger:Innen) werden dann zu RbG Folgestudien eingeladen, um die Beziehung zwischen Merkmalen und der betreffenden Genvariante besser zu erforschen.



Komplexe Krankheiten: komplexe Ursachen?!

Komplexe Krankheiten wie z.B. Krebs oder Depressionen entstehen, wenn viele Gene in Verbindung mit dem Lebensstil und der Umwelt (wie Ernährung und Bewegung) das Risiko für die Entwicklung oder den Verlauf einer Krankheit beeinflussen. Als Beispiel, Lungenkrebs wird hauptsächlich durch Umwelteinflüsse verursacht; die meisten Fälle könnten vermieden werden, wenn die Menschen mit dem Rauchen aufhören würden. Natürlich spielt die Genetik eine Rolle, aber die Auswirkungen der Umwelt überwiegen. Das gilt auch für die meisten anderen Volkskrankheiten: Man kann mehr oder weniger prädisponiert sein, aber wenn man gesund lebt, kann man vielen Volkskrankheiten wie
z.B. Bluthochdruck (Hypertonie) entgegenwirken oder sie stark beeinflussen. Eine genetische Veranlagung oder Anfälligkeit (Prädisposition) beschreibt die Wahrscheinlichkeit, eine bestimmte Krankheit zu entwickeln.

Warum sind Recall-by-Genotype-Studien wichtig?

Viele genetische Varianten werden mit Krankheiten in Verbindung gebracht, aber oft weiß man noch nicht viel über die „ursächliche Rolle“ der genetischen Varianten. RbG-Studien können helfen, die Beziehung zwischen der genetischen Variante und der Krankheit besser zu verstehen. Im Vergleich zu anderen Studiendesigns, bei denen die Teilnehmenden nach dem Zufallsprinzip ausgewählt

werden, um aussagekräftige Statistiken zu erhalten, ist RbG effizient, da vergleichsweise weniger Teilnehmende benötigt werden.

Welche Herausforderungen gibt es bei RbG Studien?

Die Entwicklung eines Verfahrens für die RbG Einladung von Teilnehmenden zu einer
Untersuchung, ist aus ethischer, rechtlicher und sozialer Sicht eine Herausforderung. Eine Herausforderung z.B. liegt darin Fragen zur Offenlegung von Forschungsergebnissen zu klären: Wenn Teilnehmende erneut kontaktiert und eingeladen werden, was sollte ihnen mitgeteilt werden, um zu erklären, warum genau Sie ausgewählt wurden?
Vor allem bei Studien, bei welchen genetische Variationen mit unbekannten oder ungewissen Konsequenzen untersucht werden, ist sich die Wissenschaftsgemeinde noch nicht einig, wie diese Informationen kommuniziert werden sollen. Obwohl bisher nur wenige wissenschaftliche Arbeiten zu ethischen Fragen der RbG veröffentlicht wurden, haben mehrere Studien gezeigt, dass in dem Fall, in welchem die Gründe für die Einladung offen kommuniziert wurde, Teilnehmende mit einer vorhandenen Krankheit keine Bedenken hatten, zu den Studien eingeladen zu werden und die Zulassungskriterien zu verstehen. Im Gegensatz dazu gab es bei Menschen ohne die Krankheit mehr Missverständnisse über die Gründe, warum genau Sie eingeladen wurden. Darüber hinaus

könnte diese Wiedereinladung (=Recall) für potenzielle Teilnehmende eine Belastung darstellen, da Sie mit einer neuen Krankheit oder Informationen über ihr Genom konfrontiert werden. Für dieses Studiendesign braucht es also eine Balance zwischen der Vermeidung einer möglichen Belastungs der Teilnehmenden durch die Offenlegung unerwünschter oder missverstandener Informationen und der Vermeidung von Verschleierungen bei der Erklärung, warum einzelne Teilnehmende ausgesucht werden und andere nicht. Deshalb wollen wir besser verstehen wie wir zugleich Autonomie (die Grundlage der informierten Einwilligung in der heutigen Forschung), Transparenz über die vorliegende Forschung, das „Recht auf Nichtwissen“ und den Grundsatz keinen Schaden anzurichten mit RbG Studien und den dazugehörigen Einladungen respektieren können.

Ziele von den RbG Studien: Ein konkretes Beispiel in der CHRIS Studie

In den letzten Jahren hat sich gezeigt, dass bei neurogenetischen Erkrankungen der Zusammenhang zwischen Genotyp und Phänotyp komplexer ist als bisher vermutet. Als ein Beispiel für RbG-Studien stellen wir die Pilot-Studien PAREGEN 2018 und die Folgestudie PAREGEN 2022 vor. Der Fokus der RbG Studien lag auf der Untersuchung von zwei heterozygoten Varianten von Genen, bei denen die homozygoten Varianten mit Parkinson assoziiert sind. Durch die CHRIS Studie wurden zahlreiche heterozygote Träger

identifiziert und diese wurden wieder eingeladen (Recall) für die Folgestudien.

Das Tragen einer einzelnen Veränderung (heterozygoter Zustand) ist nicht zwingendermaßen krankheitsauslösend aber kann ein Risikofaktor für die Entwicklung von Parkinson darstellen. Diese heterozygoten Variantenträger:Innen zeigen aber meistens keine Zeichen der Erkrankung auf. Entweder sind die Symptome bei diesen Menschen sehr schwach oder sie weisen bestimmte Faktoren auf, die sie vor einer möglichen Erkrankung schützen oder die Krankheit tritt nur bei homozygoten Variantenträger:Innen auf.

Das Ziel der RbG-Pilot-Studien ist es, diese Zusammenhänge und Mechanismen besser zu verstehen dadurch, dass man Daten von Variantenträgern:Innen und Nicht-Träger:Innen erhebt und analysiert. Die Gruppenzugehörigkeit, also ob die einzelnen Teilnehmenden Variantenträgern:Innen oder als Nicht-Träger:Innen eingeladen wurden, wurde nicht kommuniziert da diese genetischen Varianten noch nicht gut genug erforscht sind und somit kein unmittelbarer individueller Nutzen durch diese Informationen, entsteht.

Um die vorher besprochenen Missverständnisse zu vermeiden, möchten wir mit dieser Studie besser verstehen, wie die CHRIS-Studie mit der Kommunikation und Einladung zur Teilnahme an RbG-Studien mit genetischen Variationen mit derzeit unbekannter oder schlecht verstandener Bedeutung umgehen sollte.

WER WIRD KONTAKTIERT BZW. WER WIRD NICHT KONTAKTIERT?

In CHRIS gibt es die Dynamische Informierte Einwilligung, die jederzeit geändert werden kann. Um nicht das Risiko einzugehen, die Privatsphäre der CHRIS Teilnehmenden zu verletzen (Risiko der Verletzung des Rechts auf Nichtwissen), wenn genetische Informationen bei einem erneuten Kontakt implizit offengelegt werden, werden für RbG Studien nur Teilnehmende kontaktiert, welche:

1. **zugestimmt haben, erneut kontaktiert zu werden und**
2. **zugestimmt haben, Forschungsergebnisse zu erhalten.**

Glossar

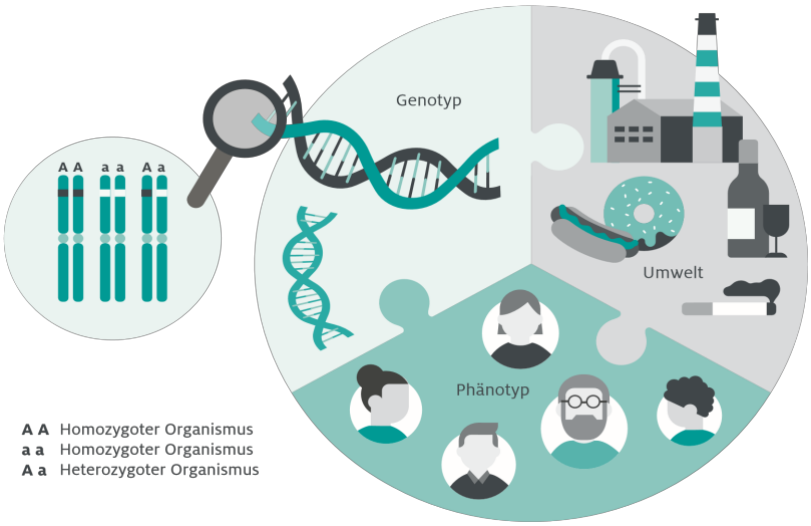
Genotyp: „genetische Ausstattung“
Genotyp nennt man die individuelle Ausstattung der Gene eines Menschen. Dieser wird erhoben mit: genetischen Screenings, die die gesamte DNA des Menschen analysieren.

Phänotyp: “Erscheinungsbild”
Der Phänotyp beschreibt sichtbare Merkmale wie z.B. Augenfarbe aber auch bestimmte Eigenschaften oder Verhaltensmerkmale. Somit bezieht sich der Phänotyp auf die Merkmale die zum (äußeren) Erscheinungsbild eines Menschen führen.
Der Phänotyp eines Menschen wird durch den Genotyp, Umwelt- und andere Lebensstilfaktoren beeinflusst.

Umwelt: Die Wechselwirkung zwischen der individuellen genetischen Ausstattung jedes Menschen und der Umwelt bedeutet, dass der Genotyp unterschiedlich auf verschiedene Umweltfaktoren reagieren kann.
Alle Merkmale sind im Erbgut, genauer gesagt auf den Chromosomen, gespeichert. Dieses Erbgut wird beeinflusst durch das Zusammenspiel von Geno-Phänotyp und der Umwelt. Es ist nicht nur der Genotyp, der den Phänotyp bestimmt, sondern auch die Umwelt und das Zusammenspiel aller Faktoren.
Heterozygot und homozygot sind Begriffe, die angeben ob ein Mensch zwei gleiche Kopien eines Gens für ein bestimmtes

Merkmal besitzt oder zwei verschiedene Kopien eines Gens für ein bestimmtes Merkmal besitzt.
Da in Menschen alle Chromosomen doppelt vorliegen, gibt es zwei Ausprägungen dieses Merkmals, eines von der Mutter und eines von dem Vater.

· Homozygot bedeutet, dass die Allele gleich sind (AA, aa)
· Heterozygot bedeutet, dass die Allele unterschiedlich sind (Aa,aA)



Chapter 3 – Survey Structure

Fragebogen über Ihre Ansichten und Vorlieben in Bezug auf Kommunikationsstrategien für Recall-by-Genotype-Studien in CHRIS

Ziel des Fragebogens ist es, Ihre Ansichten und Vorlieben zu den Kommunikationsstrategien für eine bestimmte Art von CHRIS Folgestudien namens Recall-by-Genotype Studien zu erfahren.

Es gibt keine richtigen oder falschen Antworten, wir sind einfach daran interessiert, Ihre Meinung zu erfahren

📅 Bitte füllen Sie den Fragebogen bis zum 30. April 2023 aus.

⍰ Das Ausfüllen des Fragebogens sollte ca. 10-15 Minuten dauern.

✓ Hinweis: Bitte klicken Sie auf das Kästchen, um mit dem Fragebogen zu beginnen und um anzuzeigen, dass Sie die Informationen zum Datenschutz zur Kenntnis genommen haben und zur Datenverarbeitung einwilligen.

Vielen Dank, dass Sie sich die Zeit nehmen, diesen Fragebogen auszufüllen! 💡

In dieser Umfrage sind 13 Fragen enthalten.

Eine kurze allgemeine Erklärung von Recall-by-Genotype Studien

Einleitung: Zwischen 2011 und 2018 nahmen mehr als 13.000 Personen an der CHRIS-Studie teil. Dies war die Baseline-Phase.

Diese Daten werden sicher gespeichert und für die wissenschaftliche Forschung verwendet, um Personen zu identifizieren, die zu neuen Studien wie z. B. Recall-by-Genotype-Studien eingeladen werden sollen.
Recall-by-Genotype-Studien bieten eine gezielte und effiziente Möglichkeit, genetische Forschung durchzuführen.

Angenommen, Sie werden vom CHRIS-Studienteam eingeladen, an einer Recall-by-Genotype-Studie teilzunehmen.
Frage: Wie fühlen Sie sich, wenn Sie aufgrund Ihrer Genotyp-Informationen zu einer Recall-by-Genotype-Studie eingeladen werden?
Bitte wählen Sie nur eine der folgenden Antworten aus:
☐ Komfortabel; Ich würde die Einladung begrüßen
☐ Gleichgültig; Ich habe kein bestimmtes Gefühl für die Einladung
☐ Nicht komfortabel
☐ Ich weiß es nicht
☐ Ich möchte lieber nicht antworten
Sonstiges

Frage: Was ist der Hauptgrund, warum Sie sich bei der Teilnahme wohl fühlen würden? *
Bitte wählen Sie nur eine der folgenden Antworten aus:
☐ Ich hatte eine gute Erfahrung mit CHRIS
☐ Ich empfand es als Pflicht

☐ Ich empfand ein Gefühl der Solidarität zum Wohle der Gesellschaft, zukünftiger Generationen

☐ Ich möchte einen Beitrag zur wissenschaftlichen Erkenntnis und zur Entwicklung besserer Therapien beitragen

☐ Um Wissen über meine Gesundheit zu gewinnen: wie Blut- / Urintests in CHRIS Baseline

☐ Um Wissen über die genetischen Risikofaktoren für mich oder meine Familie zu erlangen

☐ Kein besonderer Grund

☐ Ich möchte lieber nicht antworten

Sonstiges

Anleitung: Bitte wählen Sie 1 Grund aus, der zutrifft, oder geben Sie einen anderen an.

Frage: Was ist der Hauptgrund, warum Sie sich bei einer Teilnahme unwohl fühlen würden? *

Bitte wählen Sie nur eine der folgenden Antworten aus:

☐ Ich bin besorgt, dass etwas Negatives über meine Gesundheit oder die meiner Familie oder genetische Risikofaktoren herausgefunden werden könnte

☐ Ich bin besorgt darüber, nicht gut zu verstehen, worum es in der Studie geht

☐ Ich möchte mir nicht die Mühe machen oder die Zeit nehmen, ins CHRIS-Studienzentrum zu kommen

☐ Ich mag es nicht, an kleineren Studien teilzunehmen, die nicht die gesamte Kohorte umfassen

☐ Kein besonderer Grund

☐ Ich möchte lieber nicht antworten

Sonstiges

Anleitung: Bitte wählen Sie 1 Grund aus, der zutrifft, oder geben Sie einen anderen an.

Inhalt des Einladungsschreibens zur Recall-by-Genotype-Studie

Angenommen, das CHRIS-Studienteam lädt Sie ein, an einer Recall-by-Genotype-Studie teilzunehmen.

Frage: Welche Informationen möchten Sie im Einladungsschreiben VOR der Recall-by-Genotype-Studie erhalten,und wie wichtig sind die spezifischen Informationen für Sie? *

Bitte wählen Sie die zutreffende Antwort für jeden Punkt aus:

	Möchte ich auf jeden Fall wissen	Gleichgültig	Möchte ich lieber nicht wissen	Ich bevorzuge es, nicht zu antworten
Welche Krankheit wird untersucht				
Welche genetische Variante wird untersucht				
Der Grund, warum einige CHRIS-Teilnehmenden eingeladen sind und andere nicht				
Ob klinische Ergebnisse zurückgegeben werden (z. B. Blutwerte)				
Ob Informationen über genetische Risikofaktoren angeboten werden				
Ob ein Arzt zur Verfügung steht, um Fragen zu stellen				

Anleitung: Bitte wählen Sie die Wichtigkeit der verschiedenen Informationen aus.

Die mögliche Offenlegung des Trägerstatus in Bezug auf verschiedene genetische Varianten und assoziierte Krankheiten
Wie jede Studie an Menschen werfen auch Recall-by-Genotype-Studien ethische, rechtliche, soziale und gesellschaftliche Implikationen auf, die sorgfältig abgewogen und angegangen werden müssen. Eine solche Frage z.B. ist, inwieweit Studienteilnehmende darüber informiert werden sollten, welche konkrete Variante erforscht wird und ob Studienteilnehmende diese Variante tragen oder nicht.

Es gibt verschiedene Ansätze zur Offenlegung, aber letztendlich hängt die Entscheidung darüber, ob und wie genetische Informationen offengelegt werden, von den spezifischen Umständen der Recall-by-Genotype-Studie, dem ethischen und rechtlichen Rahmen und den Präferenzen der Studienteilnehmenden ab.
Information: Der persönliche Trägerstatus wird im Einladungsschreiben nicht direkt mitgeteilt, aber die Teilnehmenden erhalten Informationen über das

- Genotyp-Recall-Design,
- das Ziel der Studie,

- die untersuchte genetische Variante und
- die damit verbundene Krankheit

Mögliche Offenlegung des Trägerstatus NACH der Recall-by-Genotype-Studie

Erklärung: Genetische Varianten

Es gibt mehrere Kategorien von genetischen Varianten und deren Auswirkungen für die Gesundheit der Person. Genetische Varianten sind Unterschiede in der DNA-Sequenz, aus denen das Genom einer Person besteht. Einige genetische Varianten können das Risiko einer Person erhöhen, eine Krankheit zu entwickeln, während andere keine Wirkung haben oder sogar eine schützende Wirkung haben.

Diese Varianten können mit Umweltfaktoren interagieren, um die Wahrscheinlichkeit der Entwicklung einer Krankheit zu erhöhen oder zu verringern.

Zum Beispiel hat eine Person, die eine genetische Variante trägt, die mit einem erhöhten Risiko für Herzerkrankungen verbunden ist und raucht und Bluthochdruck hat, ein noch höheres Risiko, eine Herzerkrankung zu entwickeln als eine Person, die nur raucht und hohen Blutdruck hat.

Auf der anderen Seite sind einige genetische Varianten gutartig und beeinträchtigen die Gesundheit einer Person nicht. Diese Varianten sind in der Allgemeinbevölkerung häufig und erhöhen nicht das Risiko, an einer Krankheit zu erkranken. Schließlich können einige genetische Varianten schützend sein und das Krankheitsrisiko oder

die Wahrscheinlichkeit, eine bestimmte Krankheit zu entwickeln, verringern.

Art der genetischen Variante	**Erklärung**
Krankheitsverursachende/ Pathogene genetische Varianten	Varianten, die eindeutig mit der Entwicklung einer bestimmten Krankheit in Verbindung gebracht wurden und die Anfälligkeit oder Veranlagung einer Person für diese Krankheit erhöhen
Wahrscheinlich pathogene genetische Varianten	Varianten, die mit der Entwicklung einer bestimmten Krankheit in Verbindung gebracht werden können und die Anfälligkeit oder Veranlagung einer Person für eine bestimmte Krankheit erhöhen
Gutartige genetische Varianten	Varianten, die keine bekannten Auswirkungen auf die Gesundheit eines Individuums haben
Schützende genetische Varianten	Varianten, die mit einem reduzierten Risiko für die Entwicklung einer bestimmten Krankheit verbunden sind
Genetische Varianten von ungewisser Bedeutung/ ungewisse klinische Signifikanz	Varianten, für die nicht genügend Informationen verfügbar sind, um ihre Auswirkungen auf die Gesundheit eines Individuums zu bestimmen

Frage: Was halten Sie davon, NACH der Recall-by-Genotype-Studie, Informationen über Ihre genetischen Daten und die verschiedenen Arten von genetischen Varianten und Krankheiten zu erhalten?

Bitte wählen Sie die zutreffende Antwort für jeden Punkt aus:

	Komfortabel; Ich würde die Einladung begrüßen	Gleichgültig; Ich habe kein bestimmtes Gefühl für die Einladung	Nicht komfortabel	Ich weiß es nicht	Ich möchte lieber nicht antworten
Krankheitsverursachende/ Pathogene genetische Varianten					
Wahrscheinlich pathogene genetische Varianten					
Gutartige genetische Varianten					
Schützende genetische Varianten					
Genetische Varianten von ungewisser Bedeutung/ ungewisse klinische Signifikanz					

Anleitung: Bitte geben Sie an, was Sie davon halten, Informationen über genetische Daten zu den verschiedenen Arten von genetischen Varianten und Krankheiten zu erhalten, indem Sie das entsprechende Kästchen auf der rechten Seite ankreuzen.

Hinweis: Wenn Sie Ihre Auswahl oben erläutern möchten, gibt es an der Seite jeweils Kästchen zum Ausfüllen.

Fallstudie: Verschiedene Kommunikationsstrategien für Recall-by-Genotyp-Studien

Wir präsentieren Ihnen eine theoretische Fallstudie mit unterschiedlichen Kommunikationsstrategien, und Sie können uns sagen, was Sie darüber denken.

Es gibt verschiedene Ansätze zur Offenlegung, aber letztendlich hängt die Entscheidung darüber, ob und wie genetische Informationen offengelegt werden, von den spezifischen Umständen der Recall-by-Genotype-Studie, dem ethischen und rechtlichen Rahmen und den Präferenzen der Studienteilnehmenden ab.

Erklärung des Fallbeispiels: Einige Forschungsinstitute haben Recall-by-Genotype Studiendesigns mit Kommunikationsstrategien, bei denen die Studienteilnehmenden nicht über die Krankheit informiert werden, mit der die untersuchte genetische Variante in der Recall-by-Genotype-Studie, assoziiert wird. Sie beziehen sich auf "weitere genetische Forschung".

Frage: Wie würden Sie sich fühlen, wenn die Einladung Ihnen sagen würde, dass Sie zu "weiterer genetischer Forschung" eingeladen sind, und nicht über die genetische Variante und die Krankheit der Studie informiert werden? *

Bitte wählen Sie nur eine der folgenden Antworten aus:

☐ Sehr negativ

☐ Eher negativ

☐ Gleichgültig

☐ Eher positiv

☐ Sehr positiv

☐ Ich weiß nicht

☐ Ich möchte lieber nicht antworten

Sonstiges

Anleitung: Bitte wählen Sie 1 Antwort

Möchten Sie Ihre Antwort begründen?

Bitte geben Sie Ihre Antwort hier ein:

Wenn es noch etwas gibt, das Sie dem Team der CHRIS-Studie und dem Team des Instituts für Biomedizin mitteilen möchten, können Sie dies gerne hier tun:

Bitte geben Sie Ihre Antwort hier ein:

Informationen über Sie

Welchem Geschlecht ordnen Sie sich zu?

Bitte wählen Sie die zutreffende Antwort aus. *

Bitte wählen Sie nur eine der folgenden Antworten aus:

☐ Weiblich

☐ Männlich

☐ Anderer nicht-binärer Eintrag

Wann sind Sie geboren?

Geben Sie bitte Ihr Geburtsdatum ein. *

Bitte alle Teile des Datums eingeben!

Antwort muss zwischen 01.01.1920 und 31.12.2000 sein

Bitte ein Datum eingeben:

Ende der Umfrage

Vielen Dank, dass Sie sich die Zeit genommen haben den Fragebogen auszufüllen.