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LIIS LEITSALU

Communicating genomic research results to population-based biobank participants

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Communicating genomic research results to population-based biobank participants

UNIVERSITY OF TARTU
Press

Institute of Molecular and Cell Biology, University of Tartu, Estonia

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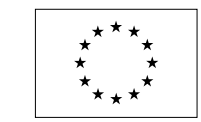

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In memory of Ewald Quak

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by Roman numerals (Ref. I to Ref. VI). Additionally, the thesis includes some unpublished data.

I. **Leitsalu L**, Alavere H, Allik A. Eesti geenivaramu kavandab tagasiside andmist geenidoonoritele. *Eesti Arst*. 92(1):9–10 (2013);

II. **Leitsalu L**, Hercher L, Metspalu A. Giving and withholding of information following genomic screening: challenges identified in a study of primary care physicians in Estonia. *J Genet Couns*. 21(4):591–604 (2012);

III. Männik K, Mägi R, Macé A, Cole B, Guyatt AL, Shihab HA, Maillard AM, Alavere H, Kolk A, Reigo A, Mihailov E, **Leitsalu L**, Ferreira A-M, Nõukas M, Teumer A, Salvi E, Cusi D, McGue M, Iacono WG, Gaunt TR, Beckmann JS, Jacquemont S, Kutalik Z, Pankratz N, Timpson N, Metspalu A, Reymond A. Copy number variations and cognitive phenotypes in unselected populations. *JAMA*. 313(20):2044–54 (2015);

IV. **Leitsalu L**, Alavere H, Jacquemont S, Kolk A, Maillard AM, Reigo A, Nõukas M, Reymond A. Männik K, Ng PC, Metspalu, A. Reporting incidental findings of genomic disorder-associated copy number variants to unselected biobank participants. *Personalized Medicine*, *13*(4), 303–314 (2016);

V. **Leitsalu L**, Haller T, Esko T, Tammesoo M-L, Alavere H, Snieder H, Perola M, Ng PC, Mägi R, Milani L, Fischer K, Metspalu A. Cohort profile: Estonian biobank of the Estonian Genome Center, University of Tartu. *Int J Epidemiol*. 44(4):1137–47 (2015);

VI. **Leitsalu L**, Alavere H, Tammesoo M, Leego E, Metspalu A. Linking a population biobank with national health registries – the Estonian experience. *J Pers Med*. 5:96–106 (2015).

My contributions to the listed publications were as follows:

Ref. II and IV	Participated in the study design, data collection, and analysis; and leading author of the paper.
Ref. III	Participated in the Estonian Biobank-specific study design; participant recruitment; and preparation and critical review of the paper.
Ref. I, V and VI	Leading author of the paper.

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LIST OF ABBREVIATIONS

ACA	Analytic validity, clinical significance and actionability
ACMG	American College of Medical Genetics and Genomics
BP	Breakpoint
BRCA	Breast cancer gene
CNV	Copy number variant
DTCGT	Direct-to-consumer genetic testing
EGCUT	Estonian Genome Center, University of Tartu
FSIQ	Full-Scale Intelligence Quotient
FSPME	Feasibility Study for Personalized Medicine in Estonia
HGRA	Human Genes Research Act
Kb	Kilobase
PCP	Primary care physician
SPSS	Statistical Package for the Social Sciences
WGS	Whole genome sequencing

INTRODUCTION

The use of genome-wide approaches to analyze human DNA sequence increases the likelihood of identifying disease-related variants. It is estimated that every whole-genome sequence contains around 10 to 50 putatively disease-related variants, with up to five being of high clinical significance (Green, Rehm, et al. 2013).

As large volumes of genomic data are generated for ever growing proportion of the population, guidelines for clinicians and researchers are needed on how to anticipate, address, and communicate incidental findings. To establish evidence-based guidelines regarding this matter open public discussions, empirical research on stakeholders' perspectives, comparison of different approaches of disclosure, as well as research on the predicted and reported impacts of communication of genomic research results to research participants are necessary (Jarvik et al. 2014).

During the currently ongoing debate, several questions have been raised:

- Should incidental findings be disclosed to research participants?
- How much and which kind of information should be disclosed?
- What is the optimal procedure for communicating incidental findings in a research practice?
- What is the impact of disclosed information?

This work addresses the issues and challenges of reporting incidental findings to the Estonian biobank participants. More specifically, the aims of the current research were to study the ethical, legal, and social implications surrounding the return of genomic research findings in the population biobank context, as well as to investigate perspectives of the general public and physicians involved in the recruitment of biobank participants. The conducted work established procedures for communicating clinically significant research results to biobank participants, and for evaluating the effects of communicating such findings.

1. REVIEW OF THE LITERATURE

1.1. Types of research results

1.1.1. Baseline assessment, aggregate and individual results

Results of population studies, including population biobank-based, longitudinal, and epidemiologic studies, can be roughly divided into three classes: data generated in baseline assessments and laboratory analyses, aggregate research results, and individual research results. Aggregate results are obtained from analyses of a group of research participants, whereas individual research results concern a particular participant (Knoppers et al. 2013; Shalowitz & Miller 2005). Communicating general results to research participants has been seen as a good practice (Beskow et al. 2012). Aggregate results can provide an overview of the use of participants' data and frequently are published in a newsletter or on a website. Communication of such general results provides means for maintaining continuous contact with participants, educating participants about the research process, affirming the value of participation, and building trust. Policy guidelines recommend that participants should be notified as quickly as possible about baseline assessment results, clinically significant laboratory findings, and, when consent permits, other analytical results (Knoppers et al. 2013).

1.1.2. Incidental findings

A research study may reveal an incidental finding, defined as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study" (Wolf et al. 2008). Incidental findings can be distinguished from individual research results because, by definition, the former are outside the scope of the study and, therefore, may be outside the researchers' focus areas or require additional clinical expertise (Christenhusz et al. 2013). When broad consent is used for genomic research, it may be difficult to distinguish individual research results from incidental findings (Wolf et al. 2008). Discovery research is open-ended by nature, with multiple unforeseen research scopes. Thus, the entire collected data can be viewed as a research result or as an incidental finding. This thesis focuses on individual genomic research findings in the context of a population biobank in which all participants signed a broad consent form for unspecified future research and will refer to these findings as incidental findings.

1.2. Debate on the return of incidental genomic findings

There is an ongoing dispute whether the uncovering of incidental findings, collectively referred to as "the incidentalome," is the future of, or a threat to, genomic medicine (Kohane et al. 2006; Biesecker 2013) (Figure 1). Some favor disclosure on the basis of autonomy, reciprocity, duty to warn, beneficence, and cost benefits (Fernandez et al. 2003; Shalowitz & Miller 2005; Knoppers et al. 2013; Belsky & Richardson 2004; Green, Berg, et al. 2013) (Affleck, 2009). Others favor nondisclosure, citing nonmaleficence ("do no harm"), right not to know, diagnostic misconception, limited resources, and the research context in which testing is done (Forsberg et al. 2009; Solberg & Steinsbekk 2012; Cho 2008; Nobile et al. 2013; Viberg et al. 2014; Kohane et al. 2006). Moreover, it is commonly unspecified what the concept "research results" entails. For example, whether only aggregate or individual results should be taken into account, and whether only validated or also preliminary research results should be considered (Miller et al. 2008). There also seems to be a tug of war between individual rights and beneficence, and collective responsibility and solidarity (Forsberg et al. 2009).

1.2.1. Arguments in favor of disclosure

Autonomy
The ethical principle of respect implies that research participants are not treated as mere means to an end (Fernandez et al. 2003). Researchers have a duty to respect the autonomy and self-determination of participants and to acknowledge their "presumptive entitlement to information about themselves" by offering requested research results (Shalowitz & Miller 2005). Health-related information would allow individuals to take control over their lives.

Reciprocity
Reciprocity regards the duty to promote trust between researchers and research participants (Knoppers et al. 2013). Based on this principle, participants are contributing to research and are entitled to receive something in return. Participants entrust researchers with their health information, putting them in a vulnerable position. Due to this entrustment, it can be argued that researchers have a duty to provide ancillary care (Belsky & Richardson 2004). It would be contradictory to point to the promise of genomics to deliver healthcare advances while ignoring detected variants of clinical importance (Biesecker 2013).

Duty to warn
Although researchers' obligations are more limited than those of clinicians, certain obligations exist. Researchers have a duty to warn participants of foreseeable harm and minimize and prevent harm to research participants (Knoppers et al. 2013).

Beneficence ("Do good")
Receiving risk information in a timely manner can reduce harms and increase benefits. This assumption is based on the premise that the to-be-disclosed findings impose substantial risk of a life-threatening condition that can be avoided or improved, or that the information could be important for reproductive decision-making.

Costs
A few researchers have argued that, given the investments made in research, it would be wasteful to disregard or discard findings other than the primary findings. In order to maximize research output, the primary study protocol should include a plan to study the clinical utility of reporting incidental findings and the long-term outcomes of these "incidental cohorts" (Biesecker 2013).

1.2.2. Arguments in favor of nondisclosure

Nonmaleficence ("Do no harm")
Disclosure of incidental findings can be harmful if they have questionable analytic or clinical validity and/or no actionability. Research results on an individual level can have questionable analytical or clinical validity because research laboratories do not have the same standards of practice as clinical laboratories. Whereas researchers seek generalizable knowledge, clinicians seek to provide health information and clinical care. Incidental findings may be outside the area of expertise of the research team, which may be ill-equipped and not licensed to provide health-related services and may require external clinical expertise to evaluate and communicate findings. There is a risk of causing a negative psychological response when participants do not know how to respond or interpret the complex information that is received.

Autonomy ("Right not to know")
For some individuals, knowledge of a clinically significant genetic finding may be burdensome. Just as autonomy, the self determination of an individual, is an argument for providing the option of disclosing information, there must be a corresponding option for not knowing (Andorno 2004).

Research context
The definitive purpose of research is to produce generalizable knowledge. Many pro-nondisclosure statements assume that participants should understand the intended output (i.e., common good and improved healthcare in the future) when contributing to biobank research. As articulated by Forsberg et al., "If potential donors are informed from the outset that there will be no direct personal gain from donating samples, and that individual results will not be returned, but that resources will be allocated to gaining as much general knowledge as possible, there need be no risk of individuals donating samples in

the hope of personal benefit" (Forsberg et al. 2009). Furthermore, the patient-physician relationship is different from the participant-researcher relationship. In the former, the patient's primary intention is to get help or knowledge from the physician, who has the training and intention to provide care (Solberg & Steinsbekk 2012). In contrast, the primary intention in the research context is to maximize research output; there is no duty to disclose.

Diagnostic misconception

It is important to consider what the communication of results represents in context of the participant-researcher relationship and how it might create a conflict of interest (Cho 2008). Communicating clinically significant incidental findings to research participants may nurture the perception that participation in research is somehow related to receiving care. In clinical research, this undue expectation is referred to as "therapeutic misconception" (Henderson et al. 2007). In genetic research, an equivalent phenomenon is called "diagnostic misconception," referring to the expectation of personal health-related information as a reward of the donation of biological material for research (Nobile et al. 2013). Based on this perception, participants might expect that research results will be accompanied by clinical management. This perception could lead to an assumption that if no results are communicated, then no disease-related information was uncovered (Viberg et al. 2014).

Limited resources

Others have questioned the potential societal benefit of communicating incidental findings. Some argue that the costs and unnecessary procedures associated with the return of incidental findings are arguments against their return (Kohane et al. 2006). In addition to the resources necessary for recontacting and validating the findings, communicating incidental findings is likely to pose a logistical challenge because most research establishments do not have the necessary infrastructure. This infrastructure includes the analytical power to find variants, and the procedures and manpower to disclose incidental findings in a manner that would improve medical care. Therefore, it could be argued that an obligation to return incidental findings would cause resources (time and money) to be spent on other than the primary goal of the research institute, thereby reducing the potential research outcome (Forsberg et al. 2009; Solberg & Steinsbekk 2012).

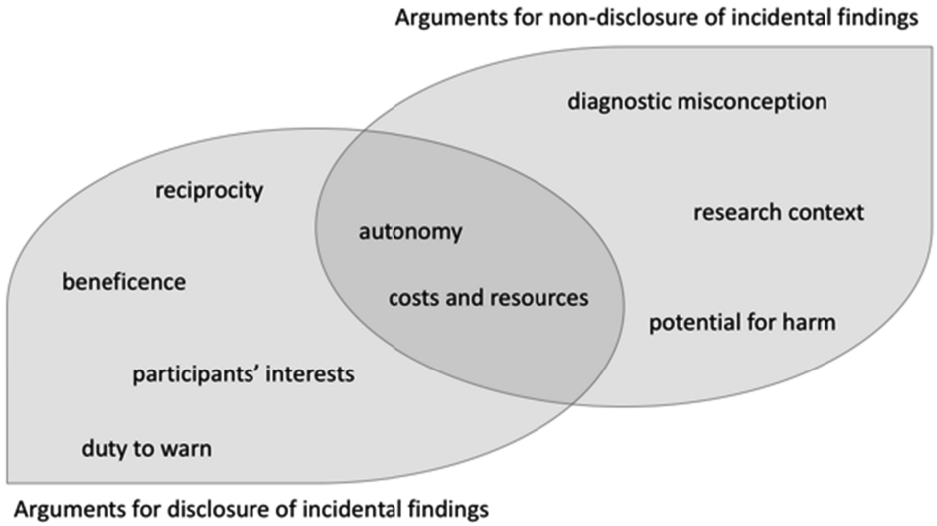

Figure 1. Arguments made supporting disclosure or nondisclosure of incidental findings.

1.3. Biobanks and return of genomic research findings

In the debate on the ethical, legal, and social implications of disclosure of incidental findings, the central dispute concerns the differences between clinical care and research. There are also a wide range of different research contexts. Here, we focus on large-scale population biobanks, which generally include individuals with a range of existing or previous conditions, but generally without an acute disease at the time of recruitment. Research is conducted using coded personal data and collected biological samples. When compared to medical research, population biobank research involves minimal risk to participants. However, genomic research has some unique considerations, as listed in the UNESCO International Declaration on Human Genetic Data (UNESCO 2003). Specifically, genomic data:

- Can be predictive of genetic predispositions concerning individuals;
- May have important impacts on the participant's family, including offspring, extending over generations, and, in some instances, on the whole population to which the participant belongs;
- May contain information of yet-unknown significance; and
- May have cultural significance for persons or groups.

Owing to these factors, genetic data are often considered to be more sensitive, leading to discussions of whether there should be specific legislation for genetic data and genetic research. Biobanks used for genomic research may be covered by biobank-specific legislation or by more general legislation (Knoppers et al. 2015).

1.3.1. Biobank consent forms and legislation

Biobanks, defined as "the organized collection of biological samples and associated data," can vary in size, collection type, organization, management, funding, and use or purpose (Cambon-Thomsen 2004). Similarly, the consent forms and surrounding legislation vary (Knoppers et al. 2015). Traditionally, the informed consent procedure involves: 1) the adequate informing of participants as to what the research project involves, and 2) the obtaining of voluntary agreement to participate (NHGRI n.d.). Several factors complicate the consent process in population biobank research, such as the indefinite storage of samples and data, unspecified future research, recontact of participants, access to medical records, large-scale sharing of data, confidentiality and privacy, and access to research results.

For large-scale prospective population biobanks intended for long-term use for unforeseeable future projects, broad consent is generally obtained. In broad consent, only the general scope of the future research is obtained, rather than acquiring new consent for each project separately. Ethical debate surrounds the appropriateness of using this type of consent (Master et al. 2012), but it has been shown to be the preferred approach by research participants (Simon et al. 2011). Alternative consent models include categorical/qualified consent and dynamic consent, which provide more choices to the research participant. Dynamic consent accounts for the dynamic nature of research possibilities over time (Kaye et al. 2015; Steinsbekk et al. 2013). Dynamic consent utilizes information technology and allows participants to express their preferences, reassess their past decisions, and change consent in light of new circumstances and research possibilities.

Recommendations on which elements should be included in a consent form for genomic research have been published (NHGRI n.d.). These elements include: the purpose of the research; description of procedures; potential risks and benefits; confidentiality and privacy; reimbursements, costs, and commercialization; options for withdrawal from the research; alternatives to participation; and contact information of the investigator. Policies recommend that the "potential risks and benefits" section anticipate incidental findings and inform the participant of options for consultation with an external expert (e.g., genetic counselor) when appropriate. This section should also include a description of "any reasonably foreseeable risks," such as an incidental finding that turns out to be a false positive or to have an unclear or ambiguous meaning. Knowledge of a finding with clinical significance and actionability can be considered as a benefit.

Several biobanks, including the Estonian population biobank (more in Section 3.1), have been created over the last two decades. Unfortunately, the consent forms are not always "future proof". In some cases, the original baseline consent form did not address the issues that now need to be covered. The ability to reidentify and recontact participants is not a given, but it is necessary to be able to link genetic findings with identifiable information (Cambon-Thomsen 2004). Some biobanks have completely anonymous data, making the recontacting of participants impossible or consent forms with a

clause stating that the participant will not be recontacted. However, others argue that consent does not constrain researchers from their responsibility to respect participants and acknowledge their entitlement to information about themselves, particularly when that information has direct clinical implications (Shalowitz & Miller 2005). There have been a few suggestions for situations in which the initial consent form does not include options or information regarding incidental findings. Assuming that the form included consent for recontact, the "staged-consent" recommendation involves recontacting and introducing the option to consent to receiving results (Knoppers et al. 2013; Appelbaum et al. 2014).

1.4. Development of guidelines for disclosure of incidental findings

1.4.1. Required elements of a finding to be reported

Although the ethical, legal, and societal consensus is leaning towards favoring the return of some incidental findings, the challenge lies in developing a consensus on how this return should be carried out. Many proposals have listed the criteria necessary for an incidental finding to be reported (Wolf et al. 2008; Knoppers et al. 2013; Cassa et al. 2012; Fabsitz et al. 2010; Wolf et al. 2012; Thorogood et al. 2014). These proposals commonly include:

- Analytic validity – Finding is accurately and reliably identified;
- Clinical validity and significance – Finding reveals a well-recognized and significant risk of a serious condition; and
- Utility or actionability – Recognized therapeutic or preventive interventions are available for the disease or condition inferred by the finding, or knowledge of the finding has the potential to change the clinical course of the disease or condition.

Frameworks based on these so-called ACA criteria (Analytic validity, Clinical significance and Actionability) are intended to facilitate the grouping of findings into broad categories taking into account the recommendations for disclosure (Wolf et al. 2008; Berg et al. 2011) (Figure 2). However, this application of the ACA criteria can be subjective and dependent on the providers' relative value judgments of the criteria. Even experts disagree on how findings should be grouped based on the ACA criteria (Green et al. 2012). In response to these difficulties, methods have been developed to establish a more operational definition of clinically actionable findings (Goddard et al. 2013). In 2013, a working group was formed by the American College of Medical Genetics and Genomics (ACMG), and a preselected minimum list of 52 genes for return of incidental findings was created for the clinical setting, referred to as the ACMG recommendations (Green, Berg, et al. 2013). The ACMG minimum list includes known deleterious or presumed deleterious variants of medically actionable conditions, which are equivalent to Bin 1 in Figure 2.

The ACMG recommendations for reporting have been implemented in several countries, including Estonia (Anon n.d.). However, as yet there is no international consensus in neither clinical nor research contexts. There has been discussion on developing a European consensus document because genomic research projects often are funded and coordinated internationally and involve participants from several countries (Hehir-Kwa et al. 2015). Currently, the decision whether the results will be communicated depends on national policies, guidelines, and ethics committees. This approach can be problematic from the participants' viewpoint, who might be treated differently from one another in terms of feedback even within the same research project. Another discussion addresses whether recommendations such as the ACMG recommendations proposed by Green et al. (Green, Berg, et al. 2013) can be applied in a research setting, given the divergent aims and guiding principles between research and clinical care (Jarvik et al. 2014).

	Criteria:	***Clinical Utility***	***Clinical Validity***			***Unknown Clinical Implications***
Genes	Bins:	**Bin 1 Medically actionable incidental information**	**Bin 2A Low risk incidental information**	**Bin 2B Medium risk incidental information**	**Bin 2C High risk incidental information**	**Bin 3 All other loci**
	Examples:	*BRCA1/2 MLH1, MSH2 FBN1 NF1*	PGx variants and common risk SNPs	*APOE* Carrier status for recessive Mendelian disorders	Huntington Prion diseases ALS (SOD1)	
	Estimated number of genes/loci:	10s	10s (eventually 100s – 1000s)	1000s	10s	~20,000
Alleles that would be reportable (YES) or not reportable (NO) in a clinical context						
Variants	Known deleterious	YES	YES/NO [1]	YES/NO [1]	YES/NO [1]	N/A [2]
	Presumed deleterious	YES	N/A [3]	YES/NO [1]	YES/NO [1]	NO [4]
	VUS	NO	N/A [3]	NO	NO	NO [4]
	Presumed benign	NO	N/A [3]	NO	NO	NO
	Known benign	NO	NO	NO	NO	NO

Figure 2. A proposed system for "binning" of incidental findings **(**Adapted from Berg et al. 2011). N/A – not applicable; VUS – variant of uncertain significance; PGx – pharmacogenomics; SNPs – single nucleotide polymorphisms; Genes listed as examples and associated conditions: *BRCA1/2* – Hereditary breast and ovarian cancer; *MLH1* and *MSH2* – Lynch Syndrome; *FBN1* – Marfan Syndrome; *NF1* – Neurofibromatosis type 1; *APOE* – Alzheimer's disease; *SOD1* – Amyotrophic lateral sclerosis (ALS).

[1] Reporting through shared decision making with an appropriate healthcare specialist if elected by the patient.

[2] Variants in genes with unknown implications cannot be considered deleterious.

[3] By definition risk SNPs or PGx variants are either present or absent.

[4] Variants in genes with unknown clinical implications would not be reported, but would benefit from further research.

1.4.2. Procedures for disclosing incidental findings

Due to great variability among biobanks (Section 1.3.1.), it is unlikely that a single approach would be suitable for all settings (Bledsoe et al. 2012). Four different approaches are used internationally for the return of results to research participants (Knoppers et al. 2015; Thorogood et al. 2014):

- Only panels of specific genes or targeted sequences are allowed, to reduce the potential for incidental findings;
- Results can only be returned when they meet the ACA criteria;
- An ad hoc case-by-case determination; and
- No return.

There seems to be a consensus that neither a complete nondisclosure nor a complete disclosure policy is appropriate. Instead, which findings should be reported to participants, and what the procedure for communication should be depends on the particular situation. There are some practical requirements involved in the return of results, such as developing a method to recontact participants, acquiring consent for the return of results, establishing a framework for the procedure of disclosing results, and separately validating findings considered for disclosure. Findings to be disclosed must be analytically valid: that is, confirmed in a certified lab. This confirmation can be challenging, as not all research findings are available as tests in clinical labs. In such cases, it is recommended that the finding be labeled as a research finding and not a clinical finding.

Recommendations for biobanks are that they set up a process for communicating incidental findings and address the associated risks and limitations in the initial consent process. The consent form should include limitations on which kind of information is reported and what is left out. Specifically, the form should indicate that there may be other incidental findings that are not reported and some clinically significant findings that are not recognized or are ambiguous in meaning (NHGRI n.d.). Many newly established biobanks address the possibility of uncovering incidental findings in their policies and provide detailed descriptions of the communication of incidental findings in their initial consent forms (Fullerton et al. 2012; Johnson et al. 2012; Fabsitz et al. 2010).

The method of grouping findings based on categories is applied in the qualified disclosure consent procedure (Christenhusz et al. 2013; Bredenoord et al. 2011). In this procedure, only findings with confirmed clinical utility and treatment or prevention possibilities qualify for routine disclosure. Research participants can indicate their preferences, including their right not to know, for certain categories. This approach is known as elective disclosure. The goal of binning and categorizing is to set limits and increase patient autonomy by constraining the decision process (Levy 2012). When the choice is between nondisclosure and full disclosure, the general response tends to be a “reflexive response to learn everything,” which might not be a particularly informed

choice (Roche & Berg 2015). The principle of qualified disclosure is also applied in dynamic consent method (Kaye et al. 2015; Steinsbekk et al. 2013).

The capacity of a DNA sequence analysis to detect disease-causing variations in the genome depends on the analysis and filtering techniques that are used. Therefore, the question of the debate should perhaps be rephrased to whether there should be a deliberate search for clinically significant findings (Schuol et al. 2015). The search for incidental findings based on a predetermined list of clinically significant variants, known as "opportunistic screening," has been viewed as unjustified in research practice because it has "the potential to undermine the research enterprise" (Presidential Commission for the Study of Bioethical Issues 2013).

1.5. Empirical research on disclosure of return of results

1.5.1. Stakeholders' perspectives, preferences and attitudes

It is valuable to know the perceptions and attitudes of stakeholders towards biobanking, genetic research, and communication of incidental findings. As mentioned in Section 1.2.1, some argue that research results should be offered as a motivator for participation and of trust between researchers and participants. Others argue that participation in research with the primary motivation of personal gain is based on the wrong premises, as the research goal should be the collective benefit for future patients (Solberg & Steinsbekk 2012). Empirical research, however, indicates that participants' motivations often are related to individual benefits generally through the gain of knowledge from health-related information (Nobile et al. 2013). Participants are interested in receiving results. In some cases, they even expect to receive something in return for participation (Bollinger et al. 2012; Middleton et al. 2015). These expectations are likely influenced by personal beliefs and trust towards the research institution, but are also dependent on the information provided during the consent process of recruitment and their comprehension of such information.

Diverse preferences are observed among members of the public, varying from wanting to know everything possible to no interest in incidental findings (Regier et al. 2015). The high preference for information is not limited to conditions that fulfill the ACA criteria, as there is interest in results with unclear treatment options or no known health consequences (Meulenkamp et al. 2010; Bollinger et al. 2012; Facio et al. 2013; Bennette et al. 2013). Other factors beyond actionability, clinical utility, or even clinical significance are potentially viewed as relevant by participants. While participants desire to learn about a range of genomic information, significant differences have been shown between the categories of findings (Facio et al. 2013). Attitudes towards receiving results on an actionable conditions and carrier status for Mendelian diseases were significantly higher than interest towards findings related to non-actionable

conditions and findings of uncertain significance. These results highlight the significance of a more refined choice than disclosure-nondisclosure, and need to consider preferences beyond the dimensions of treatability and clinical utility. The public acknowledges that the medical relevance of incidental findings is subjective and prefers to have several options, similar to that offered by qualified disclosure or dynamic consent (Townsend et al. 2012).

Meanwhile, the public recognizes the practical problems associated with the return of incidental findings (Bollinger et al. 2012; Townsend et al. 2012). Middleton et al. reported that although most people thought that findings should be made available if participants express interest, only a minority thought it was reasonable for researchers to search actively for incidental findings if doing so might compromise their research (Middleton et al. 2015). This finding is in agreement with the ethical arguments made in Section 1.2.2 regarding the main aims of research.

Compared to the public, the views of genetic researchers and clinical professionals in the genetic health profession are more conservative, possibly due to an anticipation of an increased workload when being invited to help with the interpretation of findings and counselling (Middleton et al. 2015).

1.5.2. Predicted and reported effects of disclosure

Studies investigating participants' understanding and interpretation of genomic information, and the psychosocial and behavioral impacts of personal genome information have commonly been conducted among patients in clinical contexts (Bennette 2013) or direct-to-consumer genetic testing (DTCGT) service users (Bloss et al. 2011; Bloss et al. 2013; Francke et al. 2013; Kaufman et al. 2012). Although individuals purchasing the commercially available genomic testing service likely do not represent the population at large (with adult, white non-Hispanics, older adults, people with higher incomes and postgraduate degrees being overrepresented (Kaufman et al. 2012)). These DTCGT service users are generally healthy individuals similarly to the population study participants, in contrast to patients undergoing testing in a clinical setting likely due to a specific clinical concern.

The arguments for non-disclosure include the potential for harm. While anxiety is a key consideration among all stakeholders it may be more exaggerated among professionals compared to the public (Townsend et al. 2012). Studies conducted among DTCGT service users have suggested that genomic risk predictions for common complex diseases (low-impact variants affecting risk of common diseases) had no adverse psychological, behavioral or clinical effects on the study subjects short-term or long-term (Bloss et al. 2011; Bloss et al. 2013). Lack of evidence for long-term adverse response was also reported in a study investigating response to positive findings for hereditary breast and ovarian cancer genes, *BRCA1* and *2* (highly penetrant autosomal dominant),

among DTCGT service users (Francke et al. 2013), as well as in a population-based study (O'Neill et al. 2015).

Another argument against the disclosure of incidental findings to healthy individuals has been the potential for overwhelming the health care system with unnecessary procedures (McGuire & Burke 2008). However, results from Bloss et al. suggest that although about half of the respondents intend to undergo screening or medical tests, only a minority reported of actually doing so (Bloss et al. 2011). Similarly, an overestimation can be seen in respect to sharing results with physicians where one third of respondents reported sharing their DTCGT results with a physician, compared to the more than three quarters who predicted doing so (Kaufman et al. 2012). Thus, the potential additional burden to the healthcare system may not be as large as anticipated.

Published empirical research on the effect of disclosing individual findings to research participants is limited. However, a few ongoing research projects have been specifically designed to pilot the application of genome sequencing in medicine in order to establish evidence-based practice of genomic medicine. These include the ClinSeq and MedSeq projects launched in 2009 and 2014 respectively (Lewis et al. 2016; Vassy et al. 2014).

Within the MedSeq study, the perceived utility of whole genome sequencing (WGS) was investigated (Lupo et al. 2016). The majority of participants perceived some utility of WGS for health-related decision making, while another 23% saw utility also in relation to reproductive choices and end-of-life planning, items that can be considered to be related to personal utility. Close to a fifth of the respondents, however, were skeptical regarding the utility of WGS results in general. This skepticism seemed to be associated with limited trust towards the ability to translate WGS information in clinical practice.

In a recent report on the ClinSeq study, the reactions of participants to actionable sequencing results were reported to be positive or neutral by the majority of respondents (Lewis et al. 2016). In contrast to the results reported in DTCGT context (Kaufman et al. 2012), high rates of disclosure of findings to family members and physicians were reported in the ClinSeq study. This difference could be either due to the type of findings reported or due to differences in study settings. Although majority did not report changes to healthcare in response to sharing the genomic information, participants valued receiving the results and the majority of them were interested in receiving results in the future.

2. AIMS OF THE STUDY

The aims of the current study were as follows:

1. To evaluate the ethical, legal, and social implications and logistical challenges related to the return of individual genomic research results to Estonian population based biobank participants of the Estonian Genome Center, University of Tartu;
2. To investigate the perspectives and attitudes among the Estonian general public and physicians in regard to disclosing genomic information;
3. To establish a process for communicating individual genomic research results to population biobank participants; and
4. To investigate preferences for the return of results and to evaluate the long-term effects of disclosing an incidental genomic finding.

3. MATERIALS AND METHODS

3.1. Estonian Genomic Center of the University of Tartu (EGCUT) (Ref. V)

The Estonian Biobank, founded in the year 2000, is a population-based biobank of the EGCUT. Its main objectives, as stated in the Human Genes Research Act (HGRA), include the development of genetic research, collection of health and genetic information on the Estonian population, and implementation of genetic research results for the benefit of public health (Riigikogu 2000). The cohort size of 52,000 is about 5% of the adult population of Estonia from whom samples and health data were collected (Ref. V, Figure 1). A computer-assisted baseline survey was amended with modules added over the years (Ref. V, Table 1) as new projects were started. The final version of the questionnaire included ~330 questions.

3.1.1. Biobank legislation and consent (Ref. VI)

The HGRA was passed by the Estonian Parliament in 2000 (Riigikogu 2000). The HGRA regulates the maintenance and oversight of biobanks, the use of biobank data and samples stored in the repository, and the protection of rights of participants. As required by the HGRA, the participation is on a voluntary basis and through signing the EGCUT broad consent form. Some aspects of the HGRA and the broad consent form, were both crucial for the data collection and application for specific research purposes. These aspects are described in Ref. VI and include the ability to recontact participants, the ability to collect additional data from existing registries and databases, and the right of participants to be informed or not informed of the data that are collected and generated.

3.1.2. Recruitment and public engagement

Participant recruitment began in 2002. Recruitment was conducted via a network of primary care physicians (PCPs) throughout Estonia (Ref. V, Figure 2) and two recruitment centers, in Tallinn (primary) and Tartu (alternative). The recruiter network included 454 PCPs and 186 nurses. Overall, 56% of registered PCPs were involved with the project.

The EGCUT has investigated the general public's opinion and awareness of the biobank since 2001 (Metspalu 2004; Kaasik et al. 2011). A cohort of 1000 individuals between the ages of 15 and 74 years was surveyed through computer-assisted telephone interviewing. According to the last poll in 2014, 73% of Estonians stated that they were aware of the activities of the EGCUT. Among them, 70% strongly supported the project and only 1% were against the

project (Figure 3). Since the establishment of the biobank, three of the 52,000 participants have applied for the destruction of their tissue samples; two participants have prohibited the supplementation, renewal, and verification of their state of health descriptions stored in the biobank; and 26 participants have applied for deletion of the key that enables decoding.

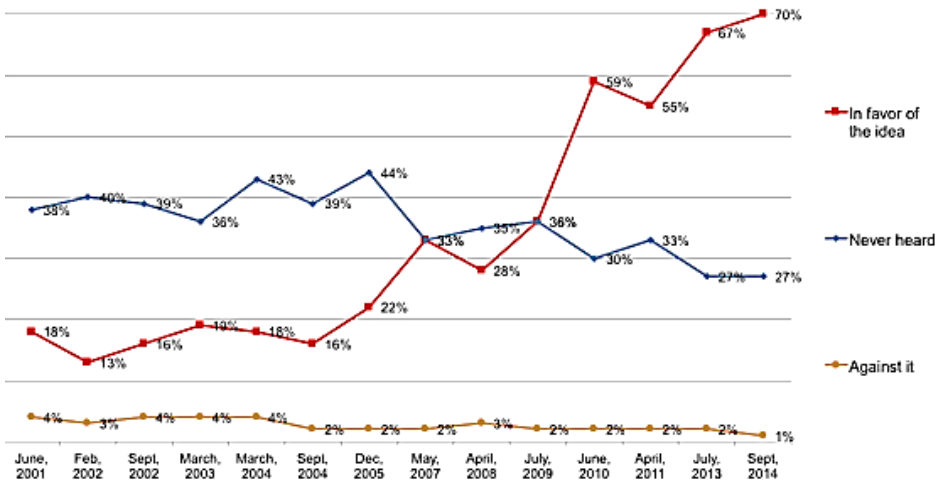

Figure 3. Public opinion and awareness of the EGCUT. Results as per the TNS Emor survey conducted since 2001 until 2014. Adapted from Kaasik et al. (Kaasik et al. 2011).

3.1.3. Recontacting and linking (Ref. VI)

The value of a biobank depends on the information accompanying the biological samples. Regularly updating health information increases the biobank's usefulness, enables researchers to conduct longitudinal and prospective studies, and allows new questions to be addressed that were not supported by the original database. Two means of acquiring new information about participants are through recontacting and through acquiring information from other existing databases and registries.

The HGRA permits the EGCUT to recontact biobank participants. Two recontacting projects were conducted. In the first project, participants were approached through their PCPs, and the response rate was 57.2%. In the second project, participants were invited though regular mail, and the response rate was 41.1% (Ref. VI). Overall, close to 2000 participants were reexamined.

Estonia, like many Nordic countries, has a long tradition of national registries. The HGRA permits the EGCUT to obtain additional information from existing databases and registries and link it with the EGCUT's biobank. This opportunity has been used regularly since 2010 (Ref. VI, Figure 1). Data were obtained from existing registries and databases for almost all participants (Ref. VI, Table 1).

3.2. Research conducted and research results (Ref. V)

Various research projects are conducted using the data and samples of the EGCUT. As of 2016, whole-exome and whole-genome sequencing data were available for 2,500 and 2,500 participants, respectively, with genome-wide genotype data being available for an additional 15,000 participants. Research results are obtained locally, or by collaborators who share results with the EGCUT once the project ends (Ref. V). The EGCUT database includes in addition to baseline assessments and lab analyses, general results, and individual research results or incidental findings. This thesis focuses on the latter.

3.2.1. Surveying PCPs

PCPs who were actively involved with participant recruitment for the EGCUT were surveyed. The survey was designed to get insight into their experience and knowledge in genetics, their perspectives regarding the use of genomic information in healthcare practice, and their interest in additional training on genetic testing (Ref. II, Appendix). The anonymous electronic survey was composed in an online survey program (Survey Monkey). The Statistical Package for the Social Sciences (SPSS) was used to analyze results.

3.2.2. Return of an incidental finding (pilot project)

For this thesis, we disclosed 16p11.2 CNV carrier status to EGCUT participants. 16p11.2 600-kb breakpoint 4 (BP4) to breakpoint 5 (BP5) deletion and reciprocal duplication carriers were identified in the EGCUT cohort. In a previous study, Jacquemont et al. investigated and characterized carriers of 16p11.2 copy-number variations (CNVs) using clinical information available in the EGCUT database (Jacquemont et al. 2011). 16p11.2 CNVs are syndromic CNVs that are commonly associated with neurodevelopmental disorders and body mass index imbalance. Extensive phenotypic variability is observed between carriers, with phenotypes ranging from almost asymptomatic to severely affected.

In agreement with the known population prevalence of 16p11.2 600-kb BP4-BP5 CNVs, four deletion carriers (0.05%) and seven duplication carriers (0.09%) were identified in the Estonian set (Jacquemont et al. 2011). The carriers of 16p11.2 CNVs identified were invited back for follow-up investigations (Ref. III) and characterized using the standardized clinical and neuropsychological protocol developed for the characterization of 16p11.2 syndromes among individuals who had been ascertained through clinical cohorts (Jacquemont et al. 2011; Zufferey et al. 2012). Procedures for recontacting participants and communicating results are described in Section 5.2.1 and Ref. IV.

A survey was developed to investigate the impact of disclosure of 16p11.2 CNVs (Ref. IV Supplementary material S4). The survey was constructed considering the outcome domains considered useful by healthcare professionals and patients (Payne et al. 2007; McAllister et al. 2011). The survey was edited after a review by working group members. Most survey questions were multiple choice questions with answers on a five-point Likert Scale (5: agree, 4: slightly agree, 3: unsure, 2: slightly disagree, 1: disagree). The sample set was too small for statistical analysis.

3.2.3. Surveying the public

To investigate the general public's attitudes towards the use of genomic information in healthcare, surveys were conducted by the polling agency TNS Emor in 2011, 2013, and 2014 (Leitsalu et al. 2012). Each year, ~1000 Estonian residents between the ages of 15 and 74 years were surveyed. The sample was composed to be proportional to the population structure with respect to age, sex, region, and nationality. Computer-assisted telephone interviewing was used for the survey. SPSS was used for data analysis. The survey included several questions adapted from previously conducted similar studies (McGuire et al. 2009; Cherkas et al. 2010; McBride et al. 2010; Bloss et al. 2011). Topics investigated in the 2011 survey included the knowledge of genetics, attitudes towards genetic testing, predicted effects on health behavior, motivators for and barriers against testing, funding of testing, and data access. In 2013 and 2014, most questions were repeated (attitudes towards genetic testing, predicted effects on health behavior, and motivators for and barriers against testing) for monitoring purposes, and a question was added about first-line genomic counseling.

3.3. Ethics

For all of the projects in this thesis involving recontacting and/or surveying of participants or physicians, ethical approval was obtained from the Research Ethics Committee of the University of Tartu.

4. RESULTS AND DISCUSSION

4.1. Communicating genomic findings in theory

4.1.1. Physicians' perspectives (Ref. II)

An anonymous electronic survey was sent to 130 PCPs, of whom 64 responded. Respondents represented a range in terms of years in practice and location. Among respondents, expectations from genetics in primary care were high: 96.4% believed that predictive genetic testing will improve health care, 73.3% believed that predictive genetic testing will be used in their practice in the next 5 years (i.e. by 2014), and 75% reported having patients who show interest in their genomic health data (Ref. II, Table 2).

Several questions addressed the conditions for which the physician would feel comfortable reporting genetic findings. Whereas 36.4% would report genetic findings under any circumstance, a majority would inform the patient under the condition that the finding is preventable (43.6%) or treatable (9.1%). There was a disagreement between responses for generic criteria questions versus specific conditions. Over 70% of respondents who selected the criterion to report only preventable or treatable conditions were willing to report about genomic findings conferring risk for Alzheimer or Huntington disease.

In sharing genomic information, PCPs expressed that they were most concerned by the "unnecessary stress caused by the risk predictions" (ranking average: 2.18) and least concerned with "stigma" (ranking average: 3.85) (Ref. II, Table 5). Responses to most options followed a normal distribution, although responses for "patient's autonomy and right not to know" (ranking average: 3.04) and for "discrimination by life insurance and other companies" (ranking average: 3.18) fell into two extremes (Figure 5.). Overall, three major themes emerged from the survey results: eagerness to apply genomic information into practice, apparent disparity between enthusiasm of using genomic information and readiness to do so, and willingness to improve the knowledge base in genetics and genomics.

This study had a possible ascertainment bias. Although survey respondents represented ~8% percent of all 804 PCPs in Estonia, they likely did not represent the general population of PCPs. They probably represented a group of physicians who were likely to have a more positive attitude towards the role of genetics in healthcare. Nevertheless, this finding indicated to us that there was a group of physicians that could be engaged in a pilot project of personalized medicine.

A similar survey was conducted among 40 healthcare practitioners (PCPs and nurses, oncologists, cardiologists, and endocrinologists) in 2015 by the Ministry of Social Affairs as part of the Feasibility Study for Personalized Medicine in Estonia (FSPME) (Anon 2015). Results of this survey were in line with the previous findings. In general, healthcare practitioners considered broader implementation of genetic information to be relevant and necessary,

and they were interested in training that would provide them with basic knowledge of genetics. Some commonly expressed fears included: 1) an increase in an already overly large workload, and 2) unnecessary worry on the part of patients, which would translate into a greater workload for the healthcare system.

It may be challenging to withhold information of medical significance once uncovered. Thus, it is necessary to have guidelines, which should preferably be more specific than categorical (i.e. a list of conditions). Ideally, the analysis pipeline would filter out findings that are not recommended to be returned, to avoid such findings from being released to the physician. The need for specific guidelines is supported by both Ref. I and the healthcare professionals surveyed in the FSPME. Physicians expressed several needs, including reasonably established processes, activities, and roles, and preparation of all stakeholders. These steps would hopefully address commonly debated questions about what stakeholder responsibilities are, who needs genetic testing (and to what extent), who decides the necessity of making genetic tests, who is responsible for interpreting test results, and how results should be interpreted (Anon 2015).

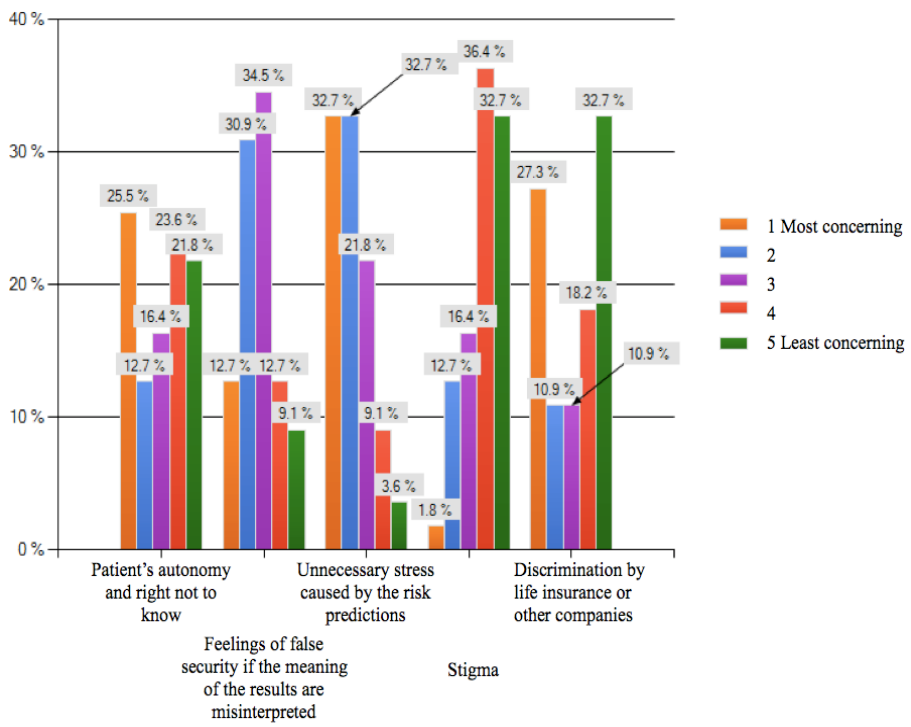

Figure 5. Primary care physicians' ranking of potential negatives associated with sharing genomic information with patients. Adapted from Ref. II, Table 5.

4.1.2. Public perspectives

From 2011 to 2013, the proportion of the public "interested" in genetic testing increased from 74% to 87%, while the proportion of "definitely not interested" remained at 7–8%. The most common motive for testing throughout the years was "So that doctors could give me better advice and monitor my health more closely," with an average of 56% agreeing with this statement. Close to half of respondents agreed with all motives for testing listed (Table 1.). The most commonly chosen barrier against testing was that the test "Might give me unwanted information," with an average of 41% agreeing with this statement. An average of 14% indicated concerns about privacy as a potential barrier against genetic testing.

In our 2011 survey, we gave participants the following statement: "Imagine you have ordered a genetic test. Based on the results, it is possible to consult you on your risks for diseases. Who should the test results preferably be sent to/shared with: your primary care physician, you, or both?" Most respondents would be willing to share the results with their PCP, either alone (14%) or with themselves (70%). Only 12% were not willing to share results with their PCP. According to a question added to the 2013 and 2014 surveys, most respondents preferred to interact with their PCP as the first contact (40%), followed by an unspecified specialist (30%), geneticist (25%), other (0%), and difficult to say (5%).

Table 1. Estonian public's motives and barriers for genetic testing*

Motive or barrier		2011	2013	2014	Mean
On average 77% very or fairly interested in testing	General curiosity about my genetic make-up	47%	53%	53%	51%
	So that I could change my lifestyle and health behavior accordingly	45%	47%	50%	47%
	So that the doctors could give me better advice and help regarding my health (monitor my health more closely)	56%	56%	55%	56%
	It could be useful for others (science, offspring)	39%	48%	46%	44%
12% not very and 8% definitely not interested	Results are not reliable, not all is known yet about the genes	24%	21%	19%	21%
	I am concerned about my privacy	20%	10%	12%	14%
	Results cannot yet be used in disease treatments	20%	16%	23%	20%
	Might give me unwanted information	40%	41%	43%	41%

*Adapted and modified from (Leitsalu et al. 2012)

In 2015, the Ministry of Social Affairs, with input from the EGCUT, conducted a more extensive survey of the public as part of the FSPME (Anon 2015). Results for potential barriers against testing were similar to those found in our survey. The most commonly raised concern was fear of unwanted/unexpected information (53%). Respondents preferred to use their PCP (37%), geneticist (29%), other specialist (20%), or web search (4%) for first-line counseling. Among all of the respondents who reported having undergone genetic testing, 79% had done so by participating in the EGCUT and the open-ended comments included disappointment about not receiving any feedback from the biobank.

Results from these surveys can be used for the development of educational resources to improve genetic literacy among the general public, to facilitate the effective use of genomic information in clinical care, and to avoid any unsound effects. Respondents indicated that they had insufficient information about what participation in the biobank entails. One of the main fears reported in all of the Estonian surveys was the fear of receiving unwanted information. These two findings support the need for additional information accompanying the consent procedure or continuous dialogue with and education of the public in general. On the flip side, most of the public indicated that they are interested in genetic testing.

4.1.3. Potential approaches for communication of findings (Ref. I)

While the discussion on whether or not to return research results to participants has been a topic of debate internationally, in the case of the EGCUT, the questions have been how and what to return. How should a population biobank with over 50,000 participants approach the preparation of individualized feedback to participants? In Ref. I, we discuss implications of two potential approaches for this challenge:

1. Public health-based approach – Conditions for feedback will be selected based on the perspective of greatest gain for the public health. Prevalent conditions causing a high burden on the national health care system would be considered first. Not all participants will have something to report, which does not necessarily mean that they do not have any clinically significant findings.
2. Individual-based approach – Search for findings to be disclosed starts from considering which findings could potentially have the most significant impact on the individual's quality of life. In this case, the utility concept considered would be broader and include personalized utility. There would be something to report for all participants.

In both approaches, the final selection of findings to be reported would have to fulfill the ACA criteria. Both approaches will pose a challenge for the research

institute and will elicit procedural and economic challenges. Besides the limitation of not disclosing genealogical information, the Estonian HGRA does not specify whether results include aggregate or individual, validated or preliminary results. One could ask then, what exactly is meant by the duty to provide results? Are there principal differences between a proactive ethical duty to offer results and a passive duty to respond positively to requests for results getting confused (Miller et al. 2008)?

In the research context, beneficence is thought to exist at the collective level, directed towards future generations; in the clinical context, beneficence is thought to be on an individual level (Forsberg et al. 2009; Solberg & Steinsbekk 2012). The public health-based approach would address one of the biobank's three objectives, namely "to use the results of genetic research to improve public health," but would fail to address the individual's right to know their research results. The individual-based approach, however, would be particularly challenging. When the selection of potential findings to be disclosed is not limited to a pre-determined list, there is a greater challenge in finding and preparing a collaborative relationship with the necessary medical specialists. Additionally, with a wide array of potential findings, informing the participant of the potential benefits and harms, and enabling them to make an informed decision, are difficult goals. This issue will be discussed in more detail in Section 4.2.1.

The EGCUT is considering implementing a participant portal. Similarly to the MyPortal of Nederland's Twin Registry (Bovenberg et al. 2009), the portal would enable participants to see if there is any genotype data generated using their sample and what projects their data have been used in. This consideration raises the issue of the aspects that participants are interested in. Survey results (see Sections 4.1.1 and 4.1.2) indicate that both the public and physicians have interest in these data. There is an understanding by participants that they took a genetic test when volunteering for the EGCUT and are now waiting for their results (Leitsalu et al. 2012; Anon 2015). This perception suggests that at least a proportion of participants are expecting individual research results. Thus, general information about the type of research conducted and the resulting publications may not fulfill their expectations.

A national personalized medicine project with biobank participants is currently in the pilot stage. Based on the public health approach, key areas were chosen for the pilot. These include cardiovascular medicine (coronary artery disease), endocrinology (type 2 diabetes) and oncology (breast cancer) (Anon 2015). In parallel, the EGCUT is conducting genotype-based research projects, wherein participants have the option to be informed of their individual research results. The first of these projects is presented in Sections 4.2.

4.2. Incidental findings and practice

4.2.1. Development of a procedure for return of results (Ref. III and Ref. IV)

Previously, the phenotype of 16p11.2 deletion and duplication carriers was described in clinically ascertained individuals – that is, patients and their relatives (Jacquemont et al. 2011). The reverse phenotyping approach, in which phenotypes are refined based on genetic marker data (Schulze & McMahon 2005), can be valuable in elucidating the spectrum of phenotypes associated with a particular genomic finding. In 2012, a project was planned to investigate the phenotype among population carriers of 16p11.2 deletions and duplications without clinical preselection: that is, through reverse-phenotyping among the population biobank cohort of the EGCUT (Ref. III).

The EGCUT has a very thorough, regularly updated database of the phenotypic health description of participants. The HGRA and consent form of the biobank enable reverse phenotyping through the abilities to link phenotype to genotype, and to recontact participants for further investigations (Ref. VI). This procedure considers the participants' rights and interests (Ref. IV). As per the HGRA, participants have a right to know or not know their research results and to be offered counseling. Prior to the 16p11.2 project, the EGCUT had not communicated any individual research findings to participants, and a procedure for communicating such findings had not been developed.

We developed a six-step process of discovery, contact, validation, feedback, follow-up, and survey, described in detail in the Methods section and illustrated in Figure 1 of Ref. IV. Discovery and validation steps were covered thoroughly in Ref. III. The key to this process was having two visits. A new separate sample was obtained for independent validation of 16p11.2 CNVs, before findings would be disclosed. The most difficult steps were recontacting participants and obtaining additional consent while not disclosing the incidental finding.

4.2.1.1. Recontacting and reconsenting

Guidelines recommend that the potential of finding incidental findings and the options regarding the communication of these findings be incorporated into the baseline consent form of prospective studies. Many biobanks have followed these recommendations (Keogh et al. 2014; Olson et al. 2013; Crook et al. 2014; Kaye et al. 2014). As most such guidelines were developed after 2010 (Knoppers et al. 2015), the situation is complex for datasets that implemented their baseline consent forms decades ago (Figure 5.), which is the case for EGCUT. Similarly, the broad consent of the EGCUT for unspecified future research included only the option to receive feedback and counseling (Ref. VI).

The situation creates a practical challenge about informed consent: How do researchers facilitate the participants to make informed choices when the nature of broad consent allows such a wide variety of research to be conducted that

even the researchers cannot predict or specify potential incidental findings? To address this question, a separate project-specific consent was prepared. This led to another challenge: How do researchers provide sufficient information within the specific consent form to enable participants to make an informed decision on disclosure of findings, without disclosing too much information? With respect to participants' right to know or not know, we decided that the invitation letter should avoid disclosing even a presence of findings. The complete invitation letter and participant information sheet can be found in Supplementary materials S1 and S2 of Ref. IV.

Wolf et al. recommended that researchers must accept participants' preference not to know. However, in the case of a finding associated with a life-threatening or very serious condition, they recommended that the researcher would reconfirm with the participant, stating: "Without revealing the information itself, the researchers may try to confirm that the research participant indeed wants to refuse even information of high health importance and utility" (Wolf et al. 2008). I would challenge this recommendation since it is itself a form of disclosure that there is a finding, leaving it up to the participant to imagine what the finding could possibly be that makes physicians double-check previously made decisions.

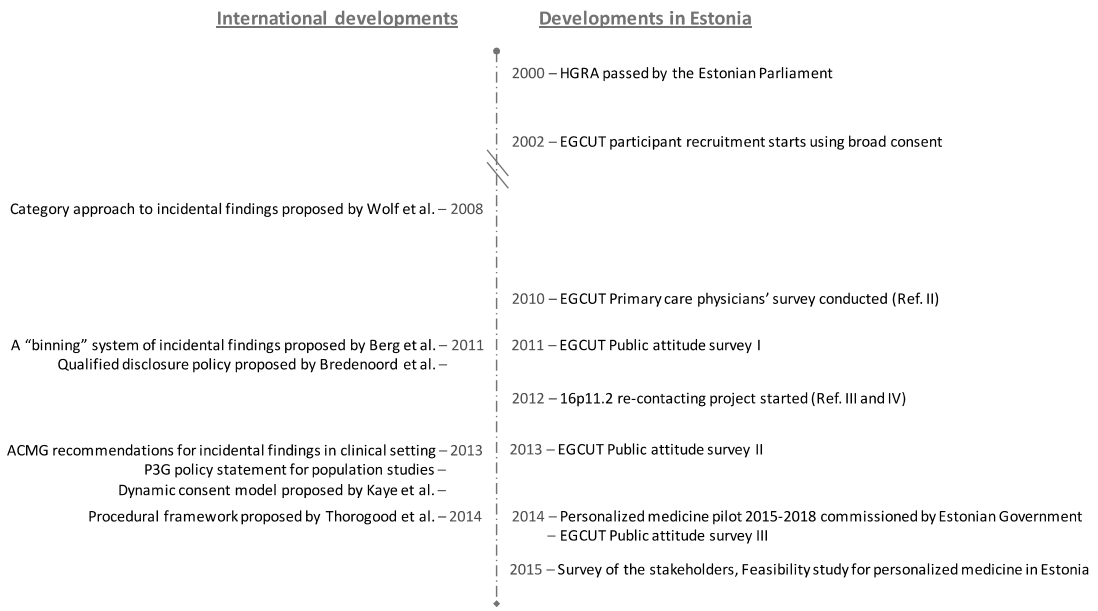

Figure 5. Timeline of key guidelines/proposals regarding the report of incidental findings and related events in Estonia.

4.2.1.2. Counseling and follow-up

There were several aspects that needed to be considered when counseling the participants. These included the fact that they are population biobank participants and not patients coming to genetic consultation *per se*; the sensitive nature of the phenotypic features associated with the conditions, the phenotypic variability of the 16p11.2 deletion and duplication syndromes and the genotype-to-phenotype approach used to identify the carriers.

The 16p11.2 deletion and duplication syndromes are both associated with psychiatric conditions (Ref. IV, Table 1.) and can be considered particularly sensitive, with a potential for stigma and discrimination. On the other hand, knowledge of a genetic origin for the psychiatric symptoms can lead to awareness that behavior is not a personal character trait but rather a symptom of a syndrome (Bortolotti & Widdows 2011).

The genotype-to-phenotype approach is valuable for describing the phenotypic variability of a syndrome. Such study type and the policy for the return of results introduce ethical issues because carriers with no apparent phenotype can receive an unexpected diagnosis. The seemingly unaffected individuals are of particular interest to researchers, but pose a particular challenge in terms of genetic counseling. As the phenotype between family members can vary from severe to seemingly unaffected it is difficult to give a prognosis and predict the severity of the phenotype. These factors may contribute to phenomenon of the "worried well", where unaffected at risk individuals behave or are treated by others as if they were ill (Bortolotti & Widdows 2011).

We offered contact details of a genetic counselor affiliated with the biobank for follow-up questions, but there was lack of interest from participants as none of them contacted the counselor. Similar results have been reported previously, with studies finding that only 10-14% of study subjects took advantage of complimentary counseling services (Bloss et al. 2011). Perhaps other means of education should be considered. In a study by Townsend et al., participants mentioned a wide range of options, with varying degrees of engagement (e.g., with professionals and self-education), to increase participants' knowledge (Townsend et al. 2012). Additionally, new communication methods and education aids are being developed that apply information and communication technologies (Sanderson et al. 2015; Bovenberg et al. 2009; Kaye et al. 2015).

4.2.1.3. Identified challenges

Main challenges in communicating research findings to biobank participants identified in this pilot study were procedural and economical, similar to those outlined by Keogh et al. and Budin-Ljoesne et al. (Keogh et al. 2014; Budin-ljøsne et al. 2016). Challenges included a lack of existing protocols, logistics, and availability of appropriate healthcare professionals. Costs and burdens involved with disclosing research results or incidental findings should be

included in the research budget from the beginning as a cost for performing ethical research (Budin-ljøsne et al. 2016).

4.2.2. Interest for disclosure and impact thereof (Ref. IV)

Previous surveys conducted in Estonia (see Sections 4.1.1 and 4.1.2) investigated stakeholders' attitudes and the hypothetical effect predicted by the general public or physicians. The EGCUT 16p.11.2 project provided an opportunity to survey the response to receiving genetic information. Although the number of participants was small, participants from the 16p11.2 project were successfully recontacted. All nine contacted individuals were interested in participating in the project (Ref. IV, Figure 1). Interest for receiving results was evident, with all eight participants who were able to participate expressing interest in the disclosure of results and counseling. These results are consistent with the results of Estonian surveys, which showed high interest for genetic testing. Similarly, previous reports showed high interest for receiving genomic research results and/or incidental findings in general (Bennette et al. 2013; Bollinger et al. 2012; Facio et al. 2013; Meulenkamp et al. 2010) and for genetic testing for conditions involving psychiatric symptoms (Wilde et al. 2010; Jones et al. 2002).

As the EGCUT was preparing for the first project involving the communication of genomic findings to participants, a survey was constructed and sent to participants who had received an incidental finding. This survey was sent 11–17 months after finding disclosure. The response rate to the survey was 62.5% (5/8 responded), with a similar average age and Full-Scale Intelligence Quotient (FSIQ) range among responders and nonresponders (Ref. IV, Table 3.). Individual survey responses can be found in Supplementary materials S5 of Ref. IV. All five responders had a positive attitude towards being contacted by the biobank and having the finding disclosed. Most felt that the information had a positive impact on their health care and/or treatment (see Perceived impact in Ref. IV, S5). Using a 5-point Likert scale, where 5 is agree and 1 is disagree, respondents indicated that the received information was interesting (mean response score of 5), informative (4.4), valuable (4.25), and understandable (4.2). Similarly to previous reports (O'Neill et al. 2015) a range of emotional response was reported. On average, the communication of results made participants feel clarity (3.8) and relief (3.6) and did not leave them indifferent (1.75). Four of the five participants reported being able to cope. Overall, there were no participants who had a completely negative response (Table 2). Two participants (Dup2 and Del3), who tended to have more negative responses, still reportedly were able to cope, were glad to be contacted, and perceived a positive change in their treatment or condition. One participant (Dup3) who was not able to cope with the finding tended to respond positively to most other questions. One could argue that the three nonresponders to the survey might be representatives of negative response, unfortunately we do not know the reasons for not responding.

Table 2. Individual participant responses post disclosure of 16p11.2 CNV carrier status. *

	Dup1	Dup2	Dup3	Del2	Del3	Mean
The information provided at the genome center and in the letter on the genetic finding and the potential health problems associated with it was:[1]						
Understandable	5	2	5	5	4	4.2
Interesting	5	5	5	5	5	5
Informative	5	4	4	5	4	4.4
Valuable	x	4	4	5	4	4.25[2]
After being counseled on the health problems associated with the genetic variant I carry made me feel…[1]						
Clarity	5	2	5	5	2	3.8
Relief	5	2	4	5	2	3.6
Indifference	x	3	2	1	1	1.75[2]
Confusion	x	4	3	1	4	3[2]
Worry	5	5	2	1	2	3
For the statement please mark the most appropriate answer[1]						
I am able to cope with having this condition in my family	5	5	1	5	5	4.2
I am glad that the genome center contacted me about the genetic finding	5	5	5	5	5	5
I now have better access to health care / specialists.	5	1	4	4	2	3.2
I feel that my treatment and/or condition has improved	5	4	3	3	5	4

[1] (5 - Agree, 4 - Slightly agree, 3 - Unsure, 2 - Slightly disagree, 1 - Disagree)
[2] Not all 5 respondents answered this question.
x – unanswered
Negative responses
*Table adapted from Ref. IV, S

In the survey, four of the five respondents reported having an appointment with their PCP. Two participants had an appointment with a specialist, as per our recommendations (Ref. IV, Table S3). Although only one person reported changes in their treatment made by physicians, all participants felt that they had better access to healthcare or that their condition/treatment had improved (Table 2). Our finding that the participants seemed to value additional factors besides those with clinical implications is consistent with previous studies (Lewis et al. 2016; Lupo et al. 2016). This supports the standpoint that the utility should be considered in a broader context and that guidelines based on ACA criteria may be too restrictive (Bollinger et al. 2012; Townsend et al. 2012).

4.2.3. Future projects

Due to the small sample size in this study, the findings are not expected to be generalizable. However, they provide evidence to inform establishing a framework for returning incidental findings to research participants. The HGRA, EGCUT broad consent, and the developed framework make it possible for the EGCUT to conduct much needed empirical research on the impact of genomic findings. In 2016, the EGCUT continued recontacting on a case-by-case basis, considering the ACMG list as the starting point. Having learned from the pilot project (Ref. IV), we have improved the consent form, and altered survey methods to include immediate response and long-term follow-up with previously validated survey instruments. Predisclosure counseling and evaluations are planned for the first meeting, and results to be communicated at the second meeting, and contact with healthcare specialists is established prior to initiation of recontacting.

In 2015, the Ministry of Social Affairs asked the Government of Estonia to carry out a Pilot Project on Personalised Medicine for 2015–2018. The goal of the pilot, as per the proposal, is "to implement personalised medicine principles into Estonian health care system and to create innovative computerized infrastructure for research and development of better targeted methods for health care and disease prevention." (Anon 2015). The pilot project involves incorporating genomic information of the EGCUT cohort in the national health information system. These plans highlight the importance and need for studies on stakeholders' attitudes, on the impact and utility of reporting genomic findings, and on analyzing procedural frameworks for communicating genomic findings to research participants and patients.

5. CONCLUSIONS

I put forward four questions concerning incidental findings in the Introduction. My thesis provides the following answers to these questions as conclusions that arose from the work performed:

1. Should incidental findings be disclosed to research participants?
   PCPs and the public have expressed an eagerness for the EGCUT to disclose results.
2. How much and what information should be disclosed?
   Theoretical attitudes of PCPs and responses to actual results from biobank participants are more liberal than existing guidelines for the return of incidental findings.
3. What is the optimal procedure for communicating incidental findings in a research practice?
   We developed a procedure for the disclosure of incidental findings to research participants of a population biobank.
4. What is the impact of disclosed information?
   Respondents indicated a positive attitude towards receiving results, even results associated with psychiatric symptoms and those with limited actionability. Moreover, disclosure was shown to impose low distress.

Existing guidelines limit the scope of data for disclosure to findings that have clear implications on the participant's clinical management. This thesis adds to the increasing body of evidence that participants are interested in information, even findings that do not have clinical significance or actionability, as some results can be personally meaningful. Our results support the recommendation of Shalowitz and Miller (Shalowitz & Miller 2005) to consider the "meaningful information" that research participants may be interested in in a broader context. Our developed framework was appreciated by participants and can be applied in future projects.

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SUMMARY IN ESTONIAN

Genoomsete teadustöötulemuste tagasiside populatsioonipõhise biopanga geenidoonoritele

Iga inimgenoomi järjestus sisaldab hinnanguliselt kümmet kuni viitkümmet tõenäoliselt patogeenset variatsiooni, millest kuni viis võivad olla kliiniliselt olulisused. Ülegenoomsete meetodite kasutamine teadustöös suurendab tõenäosust avastada nn juhuleide, mis on küll tavaliselt väljaspool konkreetse uuringu eesmärke, kuid siiski kliiniliselt olulised. Laialdane genoomiandmete genereerimine tekitab vajaduse juhiste järele, mis suunaks ja ühtlustaks juhuleidude käsitlust, vastates küsimustele – kuidas peaks ootamatult tuvastatud kliiniliselt olulise leiu puhul käituma, millistel juhtudel on uuritava isiku informeerimine õigustatud ja kuidas peaks kommunikatsioon toimuma. Seejuures tuleb arvestada teadustöö üldisi eesmärke, ressursse ning uuritavate huve ja õigusi. Tõenduspõhiste juhiste loomine eeldab avalikku arutelu, empiirilisi uuringuid huvirühmade suhtumise kaardistamiseks, samuti tagasiside meetodite analüüsi ning uuringuid juhuleidudest informeerimise mõjust osalejatele. Käesolev töö loob nende juhiste koostamise lähtealused.

Töö tulemustest järeldub, et nii perearstide kui rahva seas on huvi geneetilise informatsiooni vastu. Senised juhised keskenduvad tagasiside andmisel eelkõige kliiniliselt olulistele ja sekkumistõhusatele leidudele. Perearstide hoiakud ja Geenivaramu uuritavate hinnangud geneetilise informatsiooni suhtes osutusid liberaalsemateks kui olemasolevad soovitused ja juhised. Käesolev töö lisab tõendeid, et uuritavad hindavad geneetilise informatsiooni juures lisaks kliinilistele kaalutlustele ka muid faktoreid.

Töö käigus loodi meetod juhuleidude raporteerimiseks Geenivaramu doonoritele, mis on vastavuses Inimgeeniuuringute seaduse ja olemasolevate juhistega. Uuritavate vastukaja tagasiside osas oli positiivne isegi psühhiaatriliste sümptomitega seostatud ning piiratud sekkumistõhususega leidude puhul. Väljatöötatud meetod on kasutusel järgmistes Geenivaramu projektides, mis hõlmavad tagasiside andmist geenidoonoritele.

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2008–2010	Sarah Lawrence College, Bronxville, NY, USA Joan H. Marks Graduate Program in Human Genetics Human Genetics MSc.
2004–2008	University of Edinburgh, Šotimaa, UK School of Biology, Genetics BSc. Honours
2002–2004	Berg High School, Oslo, Norra International Baccalaureate

Teadustöö:

2010–…	Tartu Ülikooli Eesti Geenivaramu, Tartu
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Kliiniline praktika:

2016–…	Tartu Ülikooli Kliinikumi Geneetikakeskus, Tallinna üksus
2008–2010	Sarah Lawrence College, Bronxville, NY, USA Maimonides Clinical Center, Brooklyn, NY Pediaatriline ja sünnieelne geneetiline nõustamine Beth Israel Medical Center, New York, NY Onkoloogiline geneetiline nõustamine St. Luke's-Roosevelt Hospital, New York, NY Pediaatriline ja sünnieelne geneetiline nõustamine Bronx-Lebanon Hospital, Bronx, NY Sünnieelne geneetiline nõustamine

Muu kogemus:

2016–…	Tartu Ülikooli inimuuringute eetika komitee liige
2015–…	BBMRI-ERIC, Common Service ELSI töögrupi riiklik esindaja
2012–…	Tartu Ülikool, Arstiteaduskond, Meditsiiniteooria ja -eetika seminar "Geneetilise testimise eetilised aspektid"
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	March of Dimes Grant assistent
	Graduate Studies Office assistent
2001–2004	Teadusasutus SINTEF, Oslo, Norra
	Assistent rakendusliku matemaatika osakonnas

Auhinnad ja stipendiumid:

2013	Mobiilsusstipendium Euroopa Liidu Euroopa Sotsiaalfond programmi DoRa raames. Viis kuud Singapuri Genoomika Insituudis Pauline Ng töögrupis.
2011	Congress Travel Award "ICHG Young Investigator Awards", konverentsi International Congress of Human Genetics.

Publitseeritud artiklid:

Cambon-Thomsen, A., Thorisson, G. a, Mabile, L., Andrieu, S., Bertier, G., Boeckhout, M., … Zins, M. (2011). The role of a Bioresource Research Impact Factor as an incentive to share human bioresources. *Nature Genetics*, *43*(6), 503–4.

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