Return of Incidental Findings and Individual Results to Participants in the Context of Research Conducted by Direct-to-Consumer Genetic Testing Companies

Jacqueline Bradbury-Jost

Centre of Genomics and Policy

and

Biomedical Ethics Unit

Department of Human Genetics

McGill University, Montreal

October 2022

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Human Genetics

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Abstract

Direct-to-consumer genetic testing (DTC-GT) companies have created some of the largest genomic data repositories in the world by storing the genetic and phenotypic information they collect from customers. As many of these companies have ventured into research endeavors, this model has elicited numerous ethical concerns related to informed consent, privacy, and commercialization. In this study, I focused on a largely unexamined issue: the return of incidental findings and individual research results. As it is increasingly common to discover medically or personally significant information about participants during genomic research, investigators are encouraged to address this possibility when recruiting participants. To examine how this is being managed in the DTC-GT context, I analyzed the research consent forms and policies of 26 web-based companies offering genetic testing services to Canadian consumers and involved in research. This thematic analysis was informed by Canadian and international guidance for the return of findings in genomic research. Most firms indicated that they retain personal identifiers and contact information, suggesting that the disclosure of findings is feasible. However, less than a third of companies discussed the issue of potential findings in their consent documents and even fewer articulated their position on whether these results would be returned to participants. They also omitted important details regarding the return strategy, including the timing and method of communication and any criteria such as validity and actionability. To address the shortcomings identified in the analysis of DTC-GT research policies, I propose several points to consider informed by existing normative guidance and the scholarly literature.

Résumé

Les entreprises de tests génétiques directs aux consommateurs (TG-DAC) ont créé certains des plus grands dépôts de données génomiques au monde en stockant les informations génétiques et phénotypiques qu'elles recueillent auprès de leurs clients. Alors que plusieurs de ces entreprises se sont lancées dans des projets de recherche, ce modèle a suscité de nombreuses préoccupations éthiques liées au consentement éclairé, à la protection de la vie privée et à la commercialisation. Dans cette étude, je me suis concentré sur une question largement inexplorée: le retour des découvertes fortuites et des résultats de recherche individuels. Comme il est de plus en plus courant de découvrir des informations importantes sur le plan médical ou personnel au sujet des participants au cours de la recherche génomique, les chercheurs sont encouragés à envisager cette possibilité lors du recrutement des participants. Afin d'examiner la façon dont cette éventualité est gérée dans le contexte de TG-DAC, j'ai analysé les formulaires de consentement à la recherche et les politiques de 26 entreprises en ligne offrant des services de dépistage génétique aux consommateurs canadiens et participant à la recherche. Cette analyse thématique s'est appuyée sur les directives canadiennes et internationales relatives à la communication des résultats individuels de la recherche génomique. La plupart des entreprises ont indiqué qu'elles conservaient les identifiants personnels et les coordonnées, ce qui laisse supposer que la divulgation des résultats est possible. Cependant, moins d'un tiers des entreprises ont abordé la question des résultats potentiels dans leurs documents de consentement et encore moins ont formulé leur position sur la question de savoir si ces résultats seraient retournés aux participants. Elles ont également omis des détails importants concernant la stratégie de retour, y compris le moment et la méthode de communication et tout critère tel que la validité et l'applicabilité. Pour aborder les lacunes identifiées dans l'analyse des politiques de recherche de compagnies de TG-

DAC, je propose plusieurs points à considérer en m'appuyant sur les directives normatives actuelles et la littérature scientifique.

Acknowledgements

I would first like to express my sincere gratitude for the guidance of my primary supervisor, Prof. Ma'n Zawati. His expertise and patience throughout this project were invaluable for the design and implementation of my research and for my professional development. I would equally like to thank my co-supervisor, Prof. Yann Joly, for his meticulous editing, constructive feedback, and mentorship. I greatly benefited from the advice and expert input of my supervisory committee members, Prof. Jean-Baptiste Rivière, Dr. Catherine Goudie, and Prof. Carolyn Ells. I would also like to thank Terese Knoppers, whose detailed comments were instrumental when editing this thesis. A very special thank you to my family for their words of reassurance and their enthusiastic support of my academic ventures. And, of course, thank you to my friends and fellow students for their help and encouragement throughout this project and my graduate studies as a whole.

Authors' Contributions

Jacqueline Bradbury-Jost designed and implemented the research, analyzed the results, and composed the thesis. She completed this work under the supervision and financial support of Professor Ma'n Zawati. The project was also supported by the Canadian Institutes of Health Research, Genome Canada and the Terry Fox Foundation.

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List of Abbreviations

ACMG: American College of Medical Genetics and Genomics

CAGC: Canadian Association of Genetic Counsellors

CCMG: Canadian College of Medical Geneticists

CIOMS: Council for International Organizations of Medical Sciences

DTC: Direct-to-consumer

DTC-GT: Direct-to-consumer genetic testing

DTP: Direct-to-participant

EASAC: European Academies of Science Advisory Council

FEAM: Federation of European Academies of Medicine

GWAS: Genome-wide association study

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IF: Incidental finding

IRB: Institutional Review Board

IRR: Individual research result

ISBER: International Society for Biological and Environmental Repositories

NASEM: National Academies of Sciences, Engineering, and Medicine

OECD: Organisation for Economic Co-operation and Development

PCBSI: Presidential Commission for the Study of Bioethical Issues

PRE: Interagency Panel on Research Ethics

REB: Research Ethics Board

RMGA: Network of Applied Genetic Medicine

TCPS 2: Tri-Council Policy Statement, 2nd Edition

WGS: Whole genome sequencing

WHO: World Health Organization

WMA: World Medical Association

1. Introduction

1.1 Background

Private genetic testing companies started to offer their services directly to consumers two decades ago, in response to a growing interest in personal genetics among the public. Today, individuals can purchase health, ancestry, and wellness DNA reports online from hundreds of direct-to-consumer genetic testing (DTC-GT) companies worldwide.[1,2] While providing this service, the companies collect biological samples as well as self-reported information regarding their clients' health, medical history, personal traits, and lifestyle.[3] This personal data can be used for secondary purposes, particularly genetic research. In fact, many DTC-GT companies are involved in scientific research in collaboration with academic institutions, industry partners, and non-profit organizations.[4,5]

This "private biobank" model can potentially accelerate scientific discoveries and the development of novel therapies because it facilitates the recruitment of research participants, minimizing the time and money required to conduct genetic research.[3] However, it also presents its own risks and ethical challenges as it can lack adequate ethical oversight and requires participants to interpret consent documents without the assistance of health professionals.[6,4] Previous studies on the DTC-GT research model have raised concerns about the privacy and confidentiality of consumer genomic data, the ability to withdraw from research, and shortcomings in the informed consent process.[5,7,8,9]

An important question that has not received much attention is how DTC-GT companies approach the management of individual-level results when they conduct research. Indeed, it is unclear whether genetic testing companies have appropriate plans for disclosing to individual

participants significant information about them that may be revealed during research. The discovery of findings with potential health or personal implications is increasingly common during genomic research due to the large volume of data that is collected,[10] and can happen incidentally ("*incidental findings*") or as part of the research results ("*individual research results*"). For example, analysis of participant data may detect a genetic disorder or a variant conferring susceptibility to disease. International organizations and policymakers have developed a multitude of normative documents to guide researchers in managing such findings.[11] In Canada, the *Tri-Council Policy Statement* requires that researchers conducting genetic research develop a plan for managing information that may be discovered, including individual results and incidental findings, and submit this plan for research ethics board (REB) review.[12] While traditional, public biobanks generally have transparent governance frameworks and are subject to institutional oversight, consumer data repositories managed by genetic testing companies may escape such scrutiny.[6,4]

In the following section, I review the scholarly literature on the DTC-GT research model. I begin by situating it within the larger context of genomic research and discussing the strengths and weaknesses of this model from the perspective of different stakeholders. I then delve into the bioethics discourse on the topic and illustrate the gap in the literature regarding the return of research findings before coming back to my research question and outlining my objectives.

1.2 Literature Review

DTC-GT research databanks

Over the past two decades, advances in technology have made it possible to analyze very large and complex datasets, while the widespread adoption of the internet, mobile applications,

and social networking services have simplified the process of data collection. This has significant implications for privacy, with corporations collecting previously unheard-of quantities of data from consumers to improve their marketing strategies. Enhanced data collection and analysis methods are also changing institutional research. Genomic research in particular benefits from the analysis of large and diverse datasets. Traditional human genomic studies have relied on sample donations from families at risk for genetic disease or patient samples stored in clinical biobanks. However, large-scale genome-wide association studies (GWAS) are much more effective at discovering new genetic variants of interest than research on isolated families.[13] These studies require large cohorts with thousands to tens of thousands of research subjects, which is difficult to achieve through traditional recruitment strategies.[14,4]

Internet-based strategies facilitate the recruitment of numerous and diverse research participants over large distances. For instance, participants can be recruited directly from online communities specific to the disease or condition of interest, a phenomenon coined direct-to-participant (DTP) research. As others have noted, patients that form or join groups and forums online to engage with others are often highly motivated to contribute to research.[8] In fact, as discussed by Rothstein *et al.* in a 2020 publication, patient advocacy groups and citizen scientists are already engaging in unregulated health research that is participant-driven and bypasses traditional research settings and institutions by utilizing mobile applications and public data repositories.[15] DTP and participant-driven studies are especially beneficial for rare and ultra-rare disease research, as the rarity of these conditions makes it particularly challenging for investigators to recruit participants. In recent years, web-based genetic testing firms have harnessed this efficient recruitment strategy to create profitable data repositories.

Direct-to-consumer genetic testing companies are well positioned to produce research since the service they provide involves the collection of genetic material and self-reported information including demographic and phenotypic data. In fact, it has been suggested that many DTC-GT companies constitute a two-sided business model, where low-cost testing services are sold in order to accumulate vast amounts of data with significant scientific and financial value.[14,13,8,16,17,4,18] These so-called "private biobanks" have grown considerably over the past decade, recruiting far more donors than most of their public counterparts.[6] For example, 23andMe's genetic biobank and database is one of the largest in the world with over 10 million participants,[14,13,19,20] and the company has signed lucrative access agreements with dozens of pharmaceutical and biotech companies, academic institutions, and non-profit organizations.[13,21,18] 23andMe has reported that 80% of its customers consent to storing their data in this research databank.[19] Customers can also elect to respond to regular research surveys on the company website and mobile application regarding their traits, heritage, health and family history.[13] Other genetic testing firms have successfully mimicked this model, providing a potential solution to recruitment difficulties encountered in the field of genomic research.[6]

Industry, academic and consumer perspectives

The different stakeholder groups of DTC-GT research each have their own perspective on the strengths and shortcomings of this emerging research model. From the point of view of genetic testing companies, selling access to a privately-owned research database greatly increases the economic viability of their business model. As demand for personal genome services plateaus, deals with pharmaceutical and biotech companies may become more lucrative than test kit sales. In 2018, GlaxoSmithKline agreed to invest $300M in 23andMe over four years for exclusive access to its genetic database for drug target discovery, and the partnership

was extended earlier this year for an additional $50M.[22,23] By contrast, 23andMe charges $99 to $199 per test kit and sales have declined unexpectedly in recent years, leading to significant layoffs in early 2020.[24] Although the company reported 1.5 million new customers in the last fiscal year,[25] it remains to be seen how many more people will be interested in purchasing personal genomics services in the years to come. Data access agreements may help ensure the viability of the business in the long term. As noted by Allyse in a 2013 commentary, the research side of personal genomics businesses may also generate additional value if it results in patentable discoveries.[16] On top of the financial reasons to engage in biobanking, some DTC-GT leaders are keen to contribute to research and to foster innovation. Anne Wojcicki, cofounder and CEO of 23andMe, has stated on multiple occasions that she is confident that the data they collect is of comparable quality to data acquired in traditional research settings and that their recruitment methods allow them to conduct research more efficiently.[8,13]

While genetic testing companies have been eager to join the world of health research, they have been resistant to external ethics oversight, a vital component of studies conducted in traditional research settings. For instance, 23andMe encountered resistance from editors when submitting a publication to PLoS Genetics in 2009 because they did not follow the ethics review requirements for human subjects research. Although the company eventually partnered with an independent IRB, they still maintained that their work did not technically require ethics review as researchers only had access to deidentified data, which is not considered human subjects research according to the *Common Rule*.[13,8]

In light of controversial data uses and partnerships with industry, there is a growing body of literature on the phenomenon of privately-owned genetic data repositories. On the one hand, these databanks address a very real need for better datasets in genomic research.[6] They have been

able to enroll more donors than public biobanks and many can re-contact participants to continuously request more phenotypic data as research interests evolve. In some cases, company representatives can also provide valuable input for the study methodology as they have extensive knowledge of their customer base.[26] However, if not executed correctly, private sector research can undermine the public's trust in the research enterprise and negatively impact subject recruitment in the future.[16,5,9,23,27,28] Academics have highlighted various ethical issues with DTC-GT research practices, including problems related to autonomy and informed consent, privacy and confidentiality, and commercialization, which are explored in the following section. They have also expressed doubts regarding the quality of the data, particularly self-reported traits, and concerns about skewed participant demographics.[13,15,8,6] Another potential issue for institutional researchers wishing to collaborate with genetic testing companies is the perception of compromised academic objectivity and conflicts of interest.[26] This model may also impact reproducibility if private firms conducting in-house studies are reluctant to make their data available to other researchers.[27]

Scholars have made several recommendations to improve company research practices and optimize collaborations with industry. Stoeklé *et al.* suggest that companies increase transparency about their data sharing practices to maintain consumers' trust in them,[14] a recommendation that is echoed by Laestadius *et al.*, Hall *et al*. and Koch.[5,29,8] Similarly, Tobin *et al.* argue that it is in the best interest of personal genomics companies to follow existing standards for human subjects research even if this is not legally required of them. In particular, they advocate for IRB review and efforts to ensure voluntary informed consent.[7] Rothstein *et al.* make the case that biomedical research should be regulated regardless of the funding source to protect participants, researchers and the public.[15] However, they recognize the difficulty of

expanding U.S human subjects research regulations which, like the *Tri-Council Policy Statement* in Canada,[10] apply specifically to projects receiving federal funding. They recommend using a risk-based approach to determine whether traditional research ethics requirements should apply to a specific project, and propose that the NIH assist unregulated researchers in adopting best practices for human subjects research.[15] Laestadius *et al.* recommend that DTC-GT companies involved in research develop a code of conduct with input from the scientific community that incorporates transparency, accountability, and objective oversight.[5] Similarly, Niemiec and Howard suggest that commercial companies assist in developing best practice guidelines along with other stakeholders to promote adherence to accepted ethical standards for research.[9] Hall *et al.* and the European academies of science (EASAC) and medicine (FEAM) have made similar recommendations.[29,27] This type of initiative has been successful in recent years, with the Future of Privacy Forum publishing the *Privacy Best Practices for Consumer Genetic Testing Services* in 2018, a policy framework backed by leading genetic testing firms that focuses on protecting consumer privacy.[30] In the case of collaborations between industry and academia, Lehmann *et al.* contend that research objectivity can be preserved by disclosing conflicts of interest, reflecting on the implications of these conflicts, and involving multiple academic and industry partners in the project to minimize the influence of individual biases. Moreover, they argue that institutional researchers must be given control over the data analysis and the freedom to publish aggregate research results, even if these reflect poorly on the companies, in order to maintain research integrity.[26]

Although the consumer bases of genetic testing companies are large and moderately heterogenous, several studies have attempted to ascertain the views of DTC-GT consumers and the public by conducting interviews and surveys and by reviewing public discussions on online

forums. Consumer expectations of how their data will be used and shared often differ from actual company practices. In a 2016 survey of 415 individuals who had considered DTC genetic testing, 73% of respondents who purchased a test felt that they received sufficient information about how their information would be treated, compared to only 22% of respondents who ultimately decided to forgo DTC testing.[31] However, customer expectations of secondary data usage were generally inconsistent with company practices. Most participants believed that their test results would only be shared with them, with only a minority of survey respondents stating that they knew the company may use their results for research or share them with other researchers. Awareness of possible secondary data usage was higher for individuals who considered but did not purchase a test.[31] A more recent study published in 2022 with 510 survey respondents also concluded that individuals who are unwilling to undergo DTC genetic testing have significantly higher privacy concerns, and that worries about data sharing and secondary data usage can deter people from using DTC testing or even motivate tested individuals to have their information removed from company databases.[32]

One clear area of concern for some customers is whether companies intend to commercialize the results of the research. Altruism and trust are both common motivators for participating in biobank research, and presumably also for DTC-GT customers who agree to donate their data to a company research database.[33,34,28] Thus, research subjects may reconsider their choice to participate if a study appears to be profit-driven rather than aiming to produce knowledge for the public good. For instance, 23andMe received backlash from some consumers on the company's blog when it was announced that they received a patent for genetic variants associated with Parkinson's disease following a study conducted using consumer samples.[16] Customers publicly expressed feelings of disappointment and distrust because they believed the

company purposely misled them during recruitment by claiming that the research was for public benefit.[33,28]

A 2021 study by Mladucky *et al.* in which they interviewed 20 DTC-GT customers similarly found that consumers felt secondary use of data for research was acceptable but disapproved of company profit from their personal data.[35] Although participants recalled minimally reading the privacy policy of the testing company, the majority were aware of some forms of secondary usage of their data. While all participants approved of their data being used for research, many thought it would be inappropriate for companies to further profit from them by selling their data. Customers were much more comfortable with their data being used by academic institutions or the medical community as opposed to DTC-GT or pharmaceutical companies, as they perceived them to have higher research standards and altruistic motives rather than being profit-driven. Overall, the participants desired increased transparency about how their data would be used, more opportunities to opt-out of data usage, easier readability of privacy policies, and more information regarding the risks of DTC-GT.[35]

Ethical issues of DTC-GT research

Many of the ethical issues associated with DTC-GT research are not novel, however the direct-to-consumer context can add additional complexity to these problems. One of the major ethical issues that is raised in the literature is related to autonomy and informed consent. Unlike individuals who consider donating their data to a research biobank or participating in a specific research project, personal genomics customers are primarily interested in learning about their ancestry and traits. Therefore, they may not be fully aware of the ways in which their data will be used and shared when purchasing commercial testing services. When a company's intent to use customer samples or data for scientific research is only presented in their terms of service or

privacy policy, this can severely undermine the autonomy of consumers.[5,9,35,2] Indeed, Rothstein *et al.* question whether this can even be considered valid consent since it is common to agree to the stipulations of these lengthy documents without carefully reading them.[15] By contrast, using separate agreements for commercial services and for research enhances autonomy by calling attention to the proposed uses of the customer's data.[7] This increases the likelihood that consumers are properly informed before agreeing to donate their sample for research, and allows them to decline research participation while still consenting to procedures related to the purchased testing service. Voluntary participation is a fundamental condition of ethical human subjects research.[16] Because it can be challenging to obtain truly informed consent without direct contact between participants and researchers,[15] some have suggested that DTC-GT companies explore novel methods of obtaining consent.[5]

A closely related concern raised in the literature and in the news is that DTC-GT companies may not meet consumers' expectations for data privacy and confidentiality and that their privacy policies are lacking in transparency.[36,31,32,37] Because of the uniquely identifiable nature of genomic information, there is also a risk in genetic research that participants are re-identified, even if data has been stripped of identifying information such as subjects' names. Although this is not unique to DTC-GT, this means it is impossible to ensure the absolute confidentiality of customers' genetic data, particularly if it is being shared or published, even in aggregate form.[38,5,8,9]

Moreover, participants may believe that they will benefit in some way from the research, perhaps therapeutically, because from their perspective the company's primary purpose is to provide them with information about their traits, carrier status, predisposition to disease, and/or ancestry.[4] Since there is often no contact between participants and investigators in DTC-GT

research, there is no opportunity for researchers to explain the research protocol to participants, answer questions, and dispel the therapeutic misconception.[8]

Finally, it has also been noted that policy documents are sometimes ambiguous about the ownership of samples and data collected from consumers and about plans for commercialization. In addition to financially benefiting from consumer data by selling access to their data repositories, companies may profit from donated data if research results are commercialized through the creation of new testing products, diagnostics and therapies.[8] A 2017 study found that several company policies state that participants will not benefit financially from any commercialization resulting from the research.[5] As remarked in the previous section, participants may be upset by patents over the results of research that was presented to them as a community good,[13,33,28] and they may also expect some form of benefit, financial or other, for their contribution.[8,9] Recognizing this, several genomic data sharing startups have created platforms to connect individuals and researchers with the goal of handing control back to data donors.[39] These "data marketplaces" allow individuals to receive monetary incentives for contributing their data to specific studies. While this model helps to distribute benefits more fairly between institutions and participants, it raises the concern of undue inducement and of compromising the voluntariness of consent.[40,20,41]

Genetic research and the return of findings

The return of findings from DTC-GT research is another issue that is not discussed in detail in the literature but has been identified as an area for future research.[7,42] Because of the increased likelihood of discovering incidental findings or medically relevant individual results in genomic research, this possibility ought to be addressed during the initial consent procedures of genetic studies and biobanks.[11,43,44,45] Participants of the Personal Genome Project, for example,

receive access to their individual research data.[8,46] Like publicly funded researchers, investigators in private, non-traditional research settings may wish to return findings to participants.[15] Research teams may be motivated to return results as a matter of reciprocity or because of a sense of responsibility towards participants who have entrusted them with their personal information.[47,4] Empirical studies suggest that participants of genomic research, including those in a biobank setting, strongly prefer or expect to receive individual research results, especially if they are reliable and have clinical or personal utility.[48,34] However, deidentification procedures may complicate the disclosure of findings.

To protect the privacy of research participants, companies may deidentify the genetic information shared with academic or industry research teams.[9] For instance, a unique number may be assigned to each participant such that the research data accessed by investigators is not associated with personal identifiers such as a participant's name or contact information.[26,19] In this case, re-contacting individual participants would involve an extra step but would still be possible so long as the company retains the identification key. Although returning results may be feasible, many companies do not indicate whether they intend to follow up with prospective participants.[8] This raises questions about whether participants will be offered the option of receiving results with clinical significance, as discussed by Adam and Friedman in a 2016 commentary on 23andMe's collaboration with Genentech to study Parkinson's disease, which involved whole genome sequencing (WGS).[42]

1.3 Research Problem

Many direct-to-consumer genetic testing (DTC-GT) companies repurpose the personal data they have collected from consumers for scientific research. The literature on this emerging research model addresses several of its ethical issues, such as critical shortcomings in obtaining

informed consent and the risk of encountering the therapeutic misconception when one is simultaneously a customer and a research participant. However, it does not answer my research question, that is, whether such companies involved in genetic research with the data of Canadian consumers have policies for the return of findings, including individual results and incidental findings. Information about individual participants that is discovered during a study, either incidentally or as part of the research results, can have significant personal or clinical implications. Therefore, I studied the research policies of genetic testing firms to better understand how they manage the findings discovered during research. The aim of this project was to examine the current research practices of DTC-GT companies and to understand how these practices fare with the guidance outlined in the *Tri-Council Policy Statement* and other Canadian and international normative documents on the return of findings. My hypothesis was that most DTC-GT companies involved in research have a no-return policy for research findings.

1.4 Objectives

My objectives for this project were:

1. To examine the current research practices of direct-to-consumer genetic testing companies with respect to the management of findings.
2. To understand how these research practices fare with the current Canadian and international guidance on the management of findings in genetic research, and to identify some of the ethical and legal issues that could arise.
3. To provide guidance to direct-to-consumer genetic testing companies on their management strategy for findings.

2. Methods

2.1 Research Design

The two major components of this thesis project were a review of normative guidance for the return of findings, and a comparative analysis of the research policies of genetic testing companies. The project also involved a review of the literature. The purpose of the review, located in the Introduction, is two-fold: to introduce the reader to the general domain and existing literature, and to support the discussion of results by contextualizing the findings. To examine the research practices of DTC-GT companies with respect to the management of findings (Objective 1), I analyzed the consent forms and other policy documents of companies that are involved in research. This same method has been used in previous studies looking at the research activities of genetic testing firms.[5,9,49] Plans for the management of findings ought to be included in consent documents, making these a logical source of data for this project. While a survey or series of interviews may have yielded additional data, these methods were not feasible due to time constraints. To meet the second objective, I reviewed Canadian and international normative guidance for the return of findings from research and examined how the research practices of genetic testing firms compare to this guidance. Lastly, I proposed reasonable suggestions to improve the policies of DTC-GT companies, informed by existing normative guidance and the scholarly literature.

2.2 Review of the Literature and Normative Guidance

Literature search and screening

A comprehensive narrative literature review on the research activities of direct-to-consumer genetic testing firms and the return of findings from DTC-GT research was conducted

using the following search and screening parameters. Records were identified by searching the PubMed and Scopus databases. The primary search terms used were *DTC-GT*, *direct-to-consumer genetic testing*, *ethic*, and *research*. The secondary search terms were *incidental findings*, *results*, *return*, and *data privacy*. A filter was applied for records published in the last 10 years exclusively. The search was concluded April 6, 2022. Supplementary articles were also identified through citation chaining.

The search results were systematically assessed for eligibility by first screening titles and abstracts and then screening full-text articles. Publications were included if the main topic fell into one of the following categories: *direct-to-consumer genetic testing and research*, or *return of findings and results from research*. Details pertaining to the results of the literature search and screening are found in Figure 1 below.

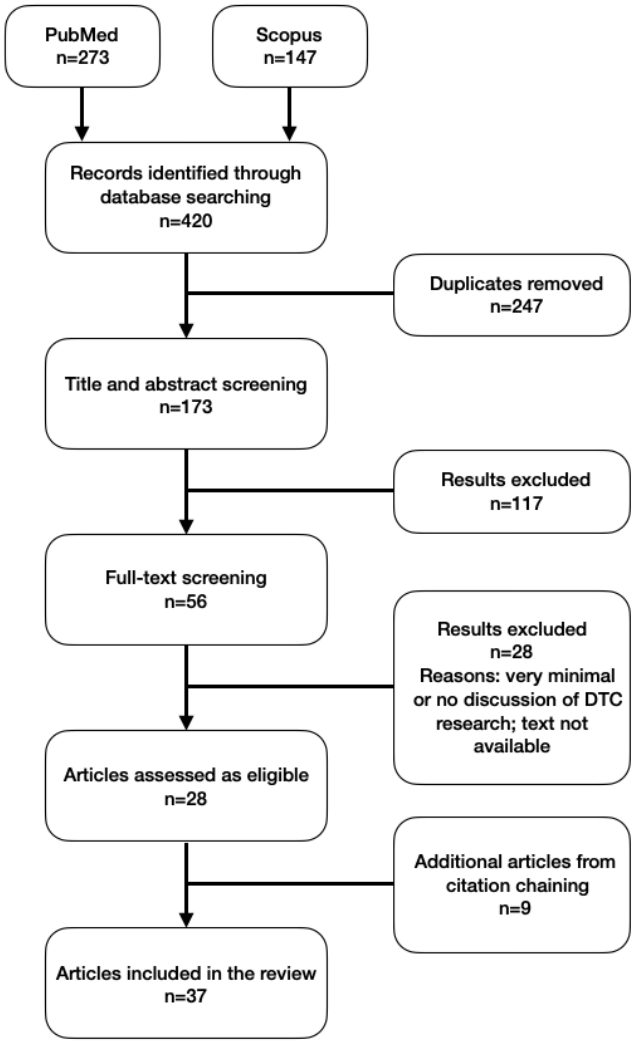

Figure 1: Flow diagram of literature screening

Identification of normative documents

Normative documents pertinent to the research question were identified by reviewing an existing compilation of laws and policies on the return of individual genomic research results.[11] This 2019 publication by Thorogood *et al*. comprehensively lists the applicable norms at the international, regional and national levels and provides a high-level summary of the approach proposed by each institution. The review of normative documents included ethical guidance and policy, but not legislation. These categories of norms are more relevant for the Canadian context

as there is no existing legislation specifically pertaining to the return of findings from research in Canada. Additional documents relevant to the Canadian context were identified through an internet search using the search engine Google, using the following terms: "return" AND "research results" OR "research findings" AND "Canada" OR "Québec". The internet search was conducted in place of a more direct database search since no suitable database of ethical guidance could be located and the HumGen database used by Thorogood *et al.* (2019) is no longer accessible. Documents published more than 15 years ago (i.e., prior to 2007) were excluded. The 2018 *Privacy Best Practices for Consumer Genetic Testing Services* published by the Future of Privacy Forum was also included as it is an important self-regulation document developed in collaboration with the DTC-GT industry.[30] The documents in Table 5 were selected for the study and informed the development of the codebook described in the comparative analysis methods.

2.3 Company Selection

Identification of companies

Two complimentary search strategies were used to identify private companies offering direct-to-consumer genetic testing (DTC-GT) services online to the Canadian public. The first strategy involved locating recent lists of companies in the DTC-GT literature. Additional companies were then found through an internet-based search strategy.

Journal articles discussing DTC-GT were identified using the PubMed database. The following search query was performed on October 20, 2021, with a filter for articles published in the last five years: (direct-to-consumer OR DTC) AND (genetic OR genome OR DNA) AND (test OR testing). The top 27 search results, out of a total of 448, were reviewed to locate

compilations of company names and/or web addresses. Due to time constraints, the screening process was ended after a sufficient number of companies for the purposes of the study (i.e. over 300) were located. Following this, an online search was performed using the search engine Google in Incognito (depersonalized) mode and the following terms: (genetic OR genome OR DNA) AND (test OR testing) AND (home OR kit OR service). This search produced 11,930,000,000 results. The first 10 pages of results (or 100 entries) were reviewed to locate companies that were not discovered in the literature search. This strategy allowed us to identify newer, smaller, and lesser-known companies that had not been included in previous studies.

Selection criteria

After compiling a list of companies, the product descriptions, "frequently asked questions," privacy policies and terms of service found on the company websites were reviewed to determine whether they would be selected for the study. Companies with inactive websites were excluded. Both consumer-ordered and physician-ordered DNA testing services were included in this study as both models raise important questions related to the secondary use of consumer data for research. DTC-GT companies identified in the literature and through the internet-based search strategy were selected for the study if they met the following inclusion criteria (Table 1). Based on a preliminary search, I expected to identify 10-15 companies corresponding to the selection criteria. The company identification and screening results are summarized in Figure 2.

Table 1: Criteria for the selection of DTC-GT companies

Inclusion criterion	**Description**	**Justification**
Direct to consumer	Test results delivered directly to the consumer	Relevant to the research goals
Genetic test category	Health-related; ancestry and genealogy; and/or lifestyle and wellness	Collect data that is useful for genetic research
Available in Canada	Can be purchased by Canadians and shipped to Canada	Relevant to the research goals
Language	Policy documents available in English or French	Research team understands these languages
Research activity	Involved in scientific research using consumer genetic data and self-reported data	Relevant to the research goals

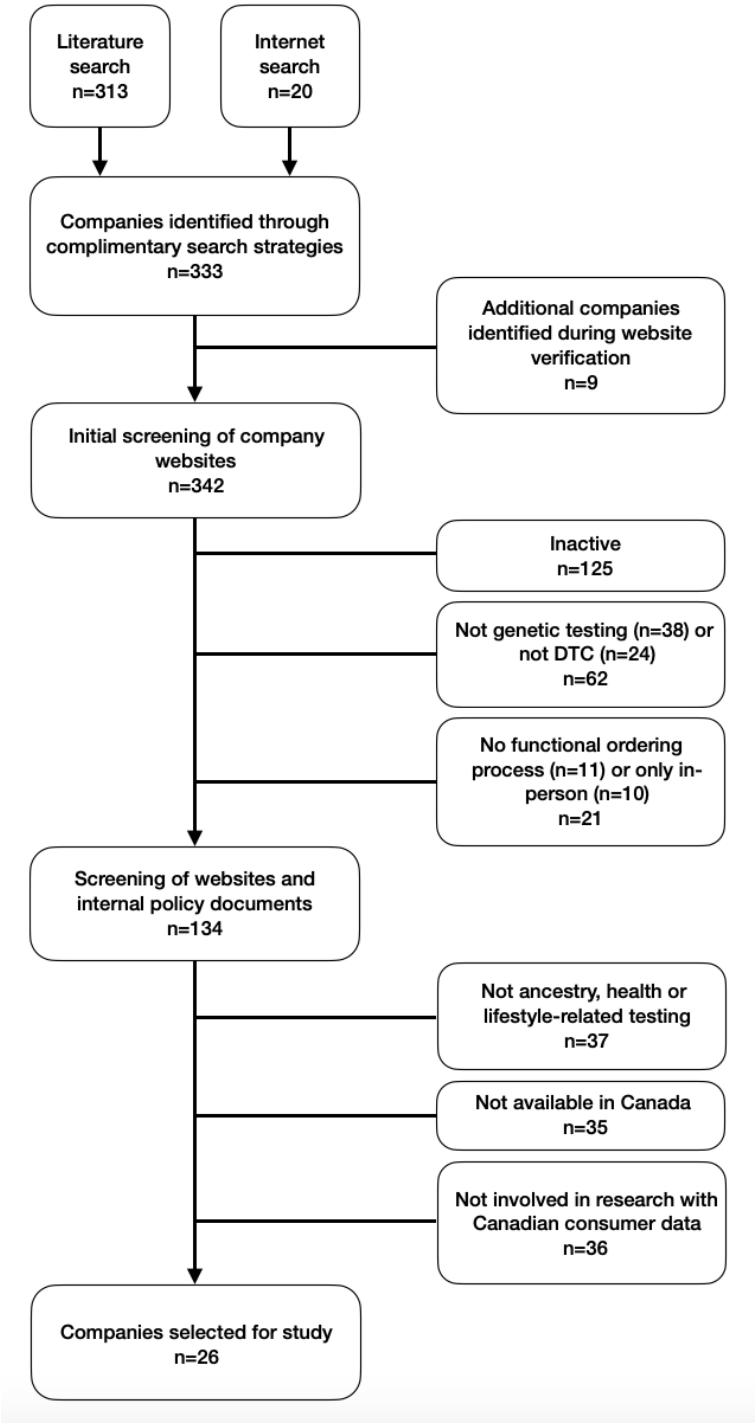

Figure 2: Flow diagram of DTC-GT company screening

The aim of this project was to study genetic testing companies that have a research component, and therefore collect data that would be useful for research. For this reason,

companies that only provide prenatal testing, paternity testing, or family relationship testing for immigration purposes were excluded from the study. Companies specializing in these categories of genetic testing have also been excluded from a 2017 study by Laestadius *et al.* on the research practices of DTC-GT companies.[5] Legal DNA testing services are very numerous, and through preliminary research I found that they generally have strict privacy policies stating that they will not share consumers' personal data for any secondary purpose. In contrast, entertainment-based services cater to consumers who are interested in genetic research and may wish to participate in studies. Moreover, paternity tests and other relationship tests are limited to 10-20 short tandem repeats (STRs) in noncoding areas of the genome,[50] whereas tests for health, genealogy and lifestyle purposes are ordinarily much broader and look at genes thought to be associated with ancestry, disease, or other personal traits. These latter tests involve whole genome sequencing (WGS) or, more commonly, screening for variants in genes of interest across the genome.[1] Many companies also collect self-reported information from consumers about their health, personal traits, and ethnicity, which can be used in conjunction with their genetic data to conduct research.[8,6]

2.4 Collection of Internal Policy Documents

The websites of the selected DTC-GT companies were closely examined in order to locate research consent forms. The links to these recruitment and internal policy documents are often provided in the "frequently asked questions" section of commercial websites or at the bottom of their webpages. If a research consent form could not be located, any other internal documents mentioning secondary data usage for research, such as privacy policies, were considered instead. The relevant document(s) for each company were downloaded and collected in a folder.

It was evident from preliminary research that, generally, privacy policies and terms of service include very little information about DTC-GT companies' research plans and return of findings policies, whereas consent forms can be much more informative. Thus, companies that did not have a consent form readily accessible on their websites were contacted in the event they could share further documents relevant to the study. Additionally, companies with broad consent forms were contacted to inquire about research consent documents or other research-specific policy documents. The company representatives were contacted using the email address, phone number or web-based contact form provided on their commercial website. If no response was received, a reminder was sent one week after the original date of correspondence.

2.5 Comparative Analysis of Internal Policy Documents

A comparative analysis of the research consent forms and other relevant policy documents was conducted to investigate the current research practices of DTC-GT companies, particularly with respect to the management of findings. Document analysis is a qualitative research method that has been used in previous studies investigating the practices of DTC-GT firms.[5,51] It involves a close reading of the selected documents to identify pertinent passages, and subsequent review to code the data and uncover themes pertinent to the research question.[52] This method allowed me to study the information provided by genetic testing companies to their consumers about their research policies and position on the return of findings. A survey or series of interviews may have yielded additional insights, but these methods were deemed less suitable given the timeline and scope of this Master's thesis; as it was sometimes challenging to obtain documents from company representatives, I expected it would be difficult to convince these companies to respond to a survey.

A codebook (see Appendix A) was developed to perform the analysis, with themes informed by guidelines in the aforementioned Canadian and international normative documents on the return of individual results and incidental findings from genetic research. A pilot study was conducted with 13 of the 26 selected companies to evaluate whether the framework of analysis was appropriate and sufficiently thorough. Subsequent adjustments and additions were made to the codebook to encompass unforeseen relevant information, and to account for a frequent lack of plans or transparency regarding the return of findings. The full document analysis was then conducted with all selected companies.

Although the primary objective of the project was to understand how DTC-GT firms manage findings from research, I first investigated how each company handled the recruitment of research participants and whether they had independent oversight to protect research participants. This information provided an initial indication of their level of respect for the autonomy of their consumers and their transparency regarding their research endeavours. Thus, I recorded the type of research consent process for each company and whether they indicated oversight by a research ethics board. To better understand the likelihood of discovering findings and the feasibility of returning these to participants, I recorded the type of data analysis conducted, level of data privacy, and intention to re-contact participants. I then examined whether the possibility of discovering findings was explained in the consent form or policy document, and the terminology used to describe potential findings. Lastly, I determined whether the documents outlined a plan for the management of findings, an option to consent to the return of findings, and details about when results would be disclosed and by whom. The complete framework can be found in Appendix A.

Each element of analysis was colour-coded to indicate whether it was a Canadian requirement. This allowed me to rapidly determine whether company policies adhered to Canadian guidelines while still including non-Canadian requirements or other elements of interest. The company consent forms were reviewed individually, and content corresponding to the codebook elements was recorded in a Microsoft Excel spreadsheet. This method was used to facilitate the identification of common patterns in policies for the return of research findings across the DTC-GT industry. In the following section, I present the results of this analysis, comparing the established guidelines for the return of findings from research to the current practices of DTC-GT companies, as indicated in their policy documents.

3. Results

3.1 Literature Review

The database searches yielded 420 results, of which 247 were duplicates, leaving 173 unique results (Figure 1). 117 records were excluded during the title and abstract screening stage. The full-text screening was then conducted with the remaining 56 records, resulting in the exclusion of 28 records. The primary reason for exclusion was a lack of discussion of DTC-GT research. A small number of records were excluded because the full text articles could not be accessed. In all, 37 papers were included in the review, of which 28 were results of the database searches and nine were identified through citation chaining. The review, located in the Introduction, is divided into four themes: background on the phenomenon of DTC-GT research databanks, perspectives and motivations of different stakeholders, ethical issues of the DTC-GT research model, and the return of findings from genetic research.

3.2 Comparative Analysis of Guidance and Norms

A total of 13 normative documents from 11 distinct institutions were reviewed to conduct the comparative analysis of guidance for the disclosure of incidental findings and individual results in genetic research. Eight documents were selected from the 2019 systematic review by Thorogood *et al*., and three additional documents were identified through the internet search described in the Methods, subsection 2.2. Also included were updated guidelines from the RMGA,[53] as well as the FPF *Privacy Best Practices for Direct-to-Consumer Genetic Testing*.[30] The FPF best practices document does not directly address the issue of returning research findings, however it does refer companies to the *Common Rule* for additional guidance regarding ethical research practices. Five of the selected normative documents are specific to the Canadian

context, while six are published by international organizations and the remaining two are policy documents of the United States. The latter two were included because they include substantial analysis and guidance regarding the return of results issue that is relevant for jurisdictions outside of the United States. Table 5 summarizes the guidance provided by each of these 13 documents for the return of findings in research.

Extent of guidance provided

While some organizations provide very specific guidance for the return of findings from research, others provide only general guidance. The recommendation with the most consensus was to articulate the research team's position on the return of findings to participants during the initial consent process; three organizations stated this must be completed, six that it should, and one that it may be done. There was also consensus between all organizations that the choice of participants to receive or reject findings ought to be respected. That said, the joint statement by the CIOMS and the WHO stated that unsolicited findings may need to be returned in "some cases." Institutions differed on their position about whether investigators had an ethical obligation to return certain findings (Table 2). Four organizations stated that research teams should or must return certain results, including material or actionable incidental findings and individual research results, and, more vaguely, "some" genetic findings. On the other hand, six organizations simply stated that investigators may return incidental findings, secondary findings, individual-level results and general research results to participants.

Table 2: Organizational positions on whether to return different types of findings from research

Type of finding	**Should or must be returned**	**May be returned**
Incidental findings	PRE RMGA	ICH WMA PCSBI
Secondary findings	none	PCBSI
Individual research results	RMGA NASEM	ISBER OECD CCMG/CAGC
Unspecified findings or results	CIOMS/WHO	WMA
Research results	none	ICH

Not all organizations articulated a position on appropriate criteria for the return of findings. Eight of the 10 institutions specified criteria that findings ought to meet if they are to be disclosed to participants (Table 3). The standards described in the normative documents were analytical validity, clinical and/or personal significance, actionability and urgency. Five organizations stated that the plan to return findings must be approved by a research ethics board.

Table 3: Organizational positions on appropriate criteria for the return of findings from research

Criteria	**Organizations**
Analytical validity	PRE, CIOMS/WHO, ICH, OECD, RMGA, CCMG/CAGC, PCSBI, NASEM
Clinical and/or personal significance	PRE, CIOMS/WHO, RMGA, CCMG/CAGC, PCSBI, NASEM
Actionability	PRE, CIOMS/WHO, RMGA, PCSBI, NASEM
Urgency	NASEM

Population-specific guidance

Many organizations touched on how to address the needs of different populations of research participants. For instance, they discussed how to approach consent for children and adolescents, and the importance of being mindful of language barriers and religious or cultural values. However, very few provided population-specific guidance for the disclosure of findings. In the Canadian context, the PRE prompts researchers to consider how to manage the consent process for participants who do not have decision-making capacity. For instance, an authorized third party ought to be designated at the outset of the study to receive any material incidental findings on the participant's behalf. Additionally, investigators should establish a process to contact participants in the event that they acquire or regain decision-making capacity. In the case of minors, guardians should be informed that they must receive findings that are actionable immediately or during childhood as they are legally required to exercise their authority in the best interest of the child.

Context or scope

Most of the normative documents focused on the management of findings in a specific context, although a few had a broader scope. The contexts of interest for this project were genetic research, biobanks and DTC tests (Table 4). Eight of the organizations provided guidance specific to genetic research, a setting which, they emphasized, comes with an increased probability of discovering findings because of the volume of data collected. Several argued that participants should be informed of this risk prior to study enrollment. They also highlighted that such findings may have implications for biological relatives of the participant due to the heritable nature of DNA. Six organizations provided guidance for biobanks or research databanks. It is notable that none of these described an ethical obligation for biobanks to return findings,

possibly because it may be less feasible to do so in this context than in smaller-scale research settings. The PCSBI and the FPF were the only organizations to offer guidance for providers of direct-to-consumer genetic tests. While the PSCBI did not address the intersection of DTC-GT firms and research, they did state that DTC-GT providers should communicate to their customers the types of results outside of the test scope that could be discovered and disclosed as well as any findings that will not be disclosed. They also argued that companies should assist in setting industry standards concerning the management of findings. The FPF did address the DTC-GT research context but did not explicitly discuss the issue of findings from research. However, in their guidelines regarding elements of informed consent for research they referred to the *Common Rule*, which requires investigators to discuss their policy for the return of clinically relevant research results with participants.[54] It is important to note that this is a revised requirement that was added to the *Common Rule* in 2018; as this is the same year that the FPF published their *Privacy Best Practices*, that requirement may not have been considered during the development of the best practices.

Table 4: Scope of guidance provided by different organizations for the disclosure of findings

Context	**Organizations**
Genetics and genomics	PRE, CIOMS/WHO, ICH, OECD, RMGA, CCMG/CAGC, PCSBI, NASEM
Biobanks and research databanks	PRE, CIOMS/WHO, ISBER, OECD, WMA, PCSBI
DTC-GT tests	PCSBI, FPF

Jurisdictional differences

In general, Canadian guidance for the management of findings was in concordance with norms at the international level. One area in which they differed was in the requirement for

ethics approval; only one of the international organizations studied, ISBER, required researchers to obtain approval from a research ethics board prior to disclosing findings to individual participants. This is a private organization. The other organizations may have omitted this requirement to accommodate for variation in national-level laws and policies on ethical oversight. The PRE was also the only organization to outline different guidance for adult and minor participants; namely, that results actionable during childhood cannot be refused by a minor's guardian.

Table 5: Normative guidance for the return of incidental findings and individual results in research

Institution	Document	Guidance
Interagency Panel on Research Ethics (PRE)	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2018)[10]	Article 3.4 on incidental findings • Within the limits of consent provided by participant • **Shall** disclose material incidental findings (IFs) • **Shall** inform participants of likelihood of discovering IFs and potential implications during consent process • **Should** provide information on strategy to disclose IFs • Guardians of minor **must** receive any IFs for child that are actionable during childhood • **Should** assist participants in understanding IFs and exercise care in determining who discloses & how • **May** request exception based on impracticability or impossibility of disclosing IFs Articles 13.2 & 13.3 on genetic research • **Shall** develop a management plan and submit to REB • **Shall** advise prospective participants of the plan • **Shall** allow participants to consent (or not) and express preferences about sharing information with biological relatives
Interagency Panel on Research Ethics (PRE)	How to Address Material Incidental Findings – Guidance in Applying TCPS 2 (2018) Article 3.4 (2018)[12]	• Material incidental findings are analytically valid, have potential significance for participant's welfare, and are actionable • Examples of justified exceptions: some population studies; research that relies on biobanks with no-return policy that participants consented to when recruited • Biobanks **encouraged** to revisit no-return policy and/or revisit consent process when they next re-contact participants • **Should** make genetic counselling available if possible • Research involving secondary use of information: **should** discuss with REB obligation to disclose material IFs and strategy to contact as contacting participants may impact their privacy and confidentiality if possibility of material IFs was not raised during consent process • **Must** report material IFs to the REB • **Should** inform participants of the limits to confidentiality due to other reporting obligations (e.g. child welfare or communicable diseases legislation)

Council for International Organizations of Medical Sciences/World Health Organization (CIOMS/WHO)	International Ethical Guidelines for Health-Related Research Involving Humans (2016)[55]	• Informed consent process for biobank **must** clearly stipulate whether return of information is foreseen, if the donor wishes • **Should** clearly state that providing individual diagnoses is not the purpose of the biobank or future research project to prevent false reassurance in the absence of unsolicited findings • There is emerging consent that at least some findings in genetic research **must** be returned to individual donors if they wish • Tiered consent gives donors a range of choices • Results **must** have analytical validity, clinical significance and actionability to qualify for being returned • **Should** evaluate whether individual counseling is necessary when returning particular genetic findings • Some cases **may** require making an ethically responsible management plan for returning (un)solicited findings
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)	Guideline on Genomic Sampling and Management of Genomic Data—E18 (2017)[56]	• Informed consent form **should** describe position on returning genomic data • **Should** articulate whether research findings and/or incidental findings will be communicated • **Should** describe timing of communication, by whom, and to whom • **Should** evaluate pertinence of genetic counselling • **Should** discuss implications of findings with subject • **Should** respect subject's consent • **Should** consider accuracy and validity of result
International Society for Biological and Environmental Repositories (ISBER)	Best Practices for Repositories I: Collection, Storage and Retrieval of Human Biological Materials for Research (2018)[57]	• **Essential** that repositories discuss return of individual research results with human subjects/ethics review committee during design of repository protocol and informed consent • Information sheet distributed to participants during consent process **may** mention return of research results
Organisation for Economic Co-operation	Guidelines on Human Biobanks and Genetic	• Participants **may** receive individual-level research results • Operators of biobank or database **should** inform participant of consequences of receiving such results

and Development (OECD)	Research Databases (2009)[58]	• **Should** inform participant of right to opt out from receiving results • **Should** explain that results may have implications for relatives • Non-validated results **should not** be reported to participants, and this **should** be explained during consent process • **Should** consider whether a trained professional should provide the feedback and/or counsel the participant
World Medical Association (WMA)	Declaration Of Taipei On Ethical Considerations Regarding Health Databases And Biobanks (2016)[59]	• Consent for storing data in health database or biobank is **only valid if** individuals have been adequately informed about procedures for return of results, including incidental findings
Network of Applied Genetic Medicine (RMGA)	Statement of Principles on the Return of Research Results and Incidental Findings (2013),[60] and Énoncé de principes consolidé du Réseau de médecine génétique appliquée du Québec (2016)[53]	• Genetic researchers **should** develop plan for managing material individual results and material incidental findings • **Should** anticipate which categories of results are likely and develop an appropriate policy for addressing them • **Should** allow participants to make an informed choice about whether to receive results • **Should** establish a policy of non-return when risks outweigh potential benefits of communicating results (e.g. findings of uncertain significance) • Individual results and IFs **should** be offered when they are material, exceptions related to research context have been weighed, REB approval obtained, participant consented, and research result has been confirmed • Individual results and IFs concerning a minor **should** be returned if actionable during childhood (parental refusal could be considered medical neglect) • **May** request exception from REB if return of individual results is impractical or impossible (eg some population research) • For longitudinal research, participants may expect results if recontacted regularly
Canadian College of Medical Geneticists &	Joint Statement on the Process of Informed Consent	• For studies in which results will be disclosed, genetic counselling **should** be a component of the consent process • **Recommended** that results ascertained in a research laboratory and returned to the research participant be validated in an accredited clinical diagnostic laboratory

Canadian Association of Genetic Counsellors (CCMG & CAGC)	for Genetic Research (2009)[61]	• If individual results are to be disclosed, research participants **should** be made aware that unexpected results could be obtained • **Should** be informed of policy with regards to disclosure of such results in the context of significant health implications for the individual and/or their family • Prior consent **should** be obtained with regard to the research participant's wish to be informed of these unanticipated results
Presidential Commission for the Study of Bioethical Issues (PCSBI)	Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts (2013)[62]	• Researchers & DTC providers **should** inform potential recipients of incidental and secondary findings that may arise or be sought from the test or procedure • Researchers **should** develop a plan for disclosing and managing these findings, and this plan **should** be reviewed and approved by an IRB • Researchers **should** convey to participants whether they can opt out of receiving certain types of findings, and how to do so • Although there is no duty to look for secondary findings in research, researchers **can** decide to look for secondary findings with approval from an IRB • DTC companies **should** communicate the types of findings that could or will be discovered and disclosed, as well as any findings that they know in advance will not be disclosed • DTC companies **should** aid in the creation of industry best practices concerning the management of incidental and secondary findings, including when and how findings will be disclosed and standards for referral to necessary clinical services
National Academies of Sciences, Engineering, and Medicine (NASEM)	Returning Individual Research Results to Participants: Guidance for a New Research Paradigm (2018)[63]	• Researchers, with oversight from their IRBs and institutions, **should** consider whether and how to return individual research results (IRRs) on a study-specific basis • Investigators or laboratories are **ethically obligated** to return urgent, clinically actionable, valid results • Investigators **should be discouraged** from returning: results that carry a risk of misinterpretation at the individual level; results that have limited value to participants and would entail significant burden to return; results without established clinical validity for a life-threatening or sensitive health condition; and results for which there are serious questions regarding validity or identity

		• Investigators **should** clarify to participants during the initial consent process: what IRRs will be offered to them, how and when these will be communicated to them, and the benefits and harms that may occur
Future of Privacy Forum (FPF)	Privacy Best Practices for Direct-to-Consumer Genetic Testing (2018)[30]	• DTC companies **should** clearly specify the uses of the genetic data, who will have access to test results, and how that data will be shared • Informed consent for research **should** include a statement concerning the confidentiality of data and description of the risks and benefits of research • Informed consent will be **required** when genetic data is transferred to third parties for research purposes and when research is done under control of the company to produce generalizable knowledge, unless otherwise approved by an IRB or internal ethical review process • Additional elements of informed consent **may apply**; see 45 CFR §46.116 o "A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions"[54] **shall** be provided when appropriate o In the case of broad consent for the secondary research use of identifiable private information or identifiable biospecimens: "Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed"[54] **shall** be provided to each participant

3.3 Company Selection

A total of 333 companies were identified using the previously described search method. 313 of these companies were identified in the literature search, and 20 were identified during the subsequent internet search. An additional nine companies were discovered while searching for the websites of already identified companies using Google, for a grand total of 342 companies. Of the 342 companies that were identified, 316 were excluded from the study (see Figure 2). Previous studies looking at genetic testing companies have had similar rates of exclusion, ranging from small, exploratory studies of a few well-established companies to more extensive studies examining the policy documents of a couple dozen companies. A systematic 2017 study by Laestadius *et al*. investigating the data practices of DTC-GT firms included 30 company websites out of the 194 that had been identified.[5] As I was specifically investigating companies involved in research, I had a higher rate of exclusion.

The reasons for exclusion were varied (Figure 2). 125 of the companies could not be found under the listed name or had inactive websites. It was confirmed that several were acquired by other genetic testing companies or had ceased operations, and it is possible that the others rebranded and changed their legal name to adapt to the dynamic market or reflect updated product offerings.[1] 38 companies were excluded because they appeared in the search even though they did not offer genetic testing. This may be because they had previously offered DNA testing or because they provided interpretation of DNA test results obtained by other DTC-GT companies. 24 companies were excluded as they did not offer tests directly to consumers but were instead clinical test providers that only delivered results to physicians. 11 company websites did not have a functional ordering process for genetic testing, and 10 more only offered testing in person. Of the remaining 134 companies, 37 were excluded because they did not offer

testing for ancestry, health, or lifestyle purposes (i.e. they exclusively offered paternity, relationship, prenatal or infidelity DNA testing), and therefore did not meet the inclusion criteria for the study. 35 companies were excluded because they did not market to Canadians. The availability of tests for Canadian consumers was determined by verifying on company websites that products could be shipped to Canada. Finally, 32 companies were excluded because they did not conduct scientific research using consumer data. The company 23andMe was excluded because it does not conduct research specifically with its Canadian consumers. However, because of the company's influence in the industry, it was analyzed as a comparator. Additionally, three companies were excluded during the document collection process after company representatives clarified that they were not actually involved in scientific research and had no plans to conduct research.

A total of 26 companies were selected for the study (listed in Appendix B). The selected companies were headquartered in eight different countries worldwide. 12 of them were headquartered in the United States, six in the United Kingdom, two in Canada, two in Spain, and one each in Hong Kong, Israel, Italy and Slovenia. The majority (n=14) of these companies offered more than one type of DNA test. 13 companies offered ancestry or genealogy testing, 18 offered health-related testing, and 15 offered DNA testing for lifestyle or wellness purposes. Two of the test providers required a physician to complete the ordering process on behalf of the consumer, with the test report still delivered directly to the consumer.

3.4 Comparative Analysis of Internal Policy Documents

Collection of internal policy documents

Using the described document collection method, I obtained nine research consent documents, seven general informed consent documents, five privacy policies and five terms of

service (including terms and conditions and terms of use). When multiple documents from one company were available, research consent forms and informed consent forms were prioritized over privacy policies and terms of service. The document(s) retrieved from each company for analysis are listed in Appendix B. There were seven genetic testing firms that had research consent forms readily available online (Table 6), and the remaining companies were contacted to inquire about research-related policy documents. I received two additional research consent forms from company representatives.

Table 6: Retrieval of consent documents from DTC-GT company websites and representatives

Type of document	**Available online**	**Obtained from representatives**	**Total retrieved**	**Declined to share**
Research consent	7	2	9	3
Informed consent (testing)	7	0	7	1

While some firms simply did not have consent forms, it is important to note that a few companies were not able to share additional existing policy documents pertaining to their research activities. Three companies were unable to share their research consent documents and one company was unable to share their general informed consent document. One company did not share a research consent form because their collaborating investigators formulate a unique consent document for every new research project. It is unclear why the other 3 companies did not wish to share their consent forms as they did not provide a reason for this decision. These firms may have general policies restricting the sharing of internal documents. This resulted in less data for the study as these unavailable documents likely contained additional information regarding company research practices, and possibly plans for the management of findings. This limitation

was most pronounced when the only documents available were terms of service or a privacy policy.

Out of the 22 genetic testing firms that were contacted, six did not respond. This could be because they had limited resources and prioritized responding to requests from their customers. They may also have had a policy of not responding to research or media requests. Alternatively, it could be due to a language barrier since the request was sent in English and two of the six companies were headquartered in Slovenia and Spain (the others being headquartered in the USA and the UK).

Analysis results

It became apparent during the pilot study (see Methods, subsection 2.5) that the consent forms and other policy documents of DTC-GT firms frequently lack any discussion of the possibility that findings with clinical or personal utility may be discovered during their research activities. To account for this, I expanded the scope of the analysis to examine elements adjacent to the return of findings, which is the primary focus of this thesis. For instance, I inferred the feasibility of returning findings by studying the capacity of DTC-GT researchers to identify and re-contact participants. To contextualize the results regarding company plans for the management of findings, I analyzed the firms' research consent processes. This helped me to discern whether the frequent lack of plans in consent documents stems from a broader disconnect from the standards and ethical principles of traditional research settings, or whether the issue of returning findings has simply been overlooked. Lastly, I studied whether companies with ethical oversight were more likely to address the disclosure of findings in consent documents.

Consent for research

The first element that was analyzed was the type of research consent process used by the testing companies. This was ascertained by the language used in the policy document, e.g. statements that consumers could "opt in" or "opt out" of participating in research, either by checking a box on the consent form, emailing company representatives, or modifying their account settings on the company website. Some documents stated that consumers would be contacted each time an opportunity to participate in a study arose, indicating a tiered consent process. For the purposes of this research project, I define tiered consent as a model where subjects can consent to specific studies as opposed to providing broad consent for the use of their data and samples in any ongoing and future studies. The documents of companies with no research consent process stated that consumer data would be stored and reused for research, and they did not provide an opportunity for consumers to opt out.

Table 7 indicates the number of companies that utilized these different methods to obtain research consent and compares it to the type of policy document they supplied to inform consumers about their research activities. These elements offer a general look at their respect for consumers' autonomy and their transparency when it comes to research, which is relevant because these are both important principles for the return of individual results and incidental findings. Tiered and opt-in consent models enable consumers to exercise their autonomy to a greater degree than opt-out models and scenarios with no consent process. Similarly, research consent documents and general informed consent forms offer more information and transparency about research activities than clauses included in privacy policies and terms of service, which are often lengthy and may not even be read by consumers.

All tabulated data regarding company documents includes only documents that were publicly available on company websites or received through correspondence with representatives, as these were available to analyze for the study. It does not include consent forms that were referenced in privacy policies, for instance, but could not be shared by representatives. The most common strategy used to obtain research consent was the opt-in method, and the least common was the opt-out method (Table 7). Companies that provided research consent forms had only tiered or opt-in consent processes, whereas companies with only general informed consent documents used opt-in and opt-out approaches. Three companies used consumer data for research without asking for separate research consent or providing an opportunity to opt out. Of note, four companies did not ask for consent to use aggregated data for publications authored solely by the company but did ask for consent for third-party research through tiered or opt-in approaches. These businesses are included in the "tiered" and "opt-in" columns of Table 7 rather than the "none" column.

Table 7: Research consent process and research-related policy document of DTC-GT companies

	Consent process for research activities				
Policy document	**Tiered**	**Opt-in**	**Opt-out**	**None**	**Total**
Research consent	1	8	0	0	9
Informed consent (testing)	0	5	2	0	7
Privacy policy	3	1	0	1	5
Terms of service	1	2	0	2	5
Total	5	16	2	3	26

Feasibility of returning findings

Next, I determined whether it was likely for companies conducting research to discover findings and feasible for them to return these findings to participants. Two relevant factors for determining the likelihood of incidental findings are the nature of the data being analyzed and

the type of analysis performed. As DTC-GT companies collect genetic data from participants, findings can be anticipated.[10] Unfortunately, most of the policy documents did not specify what type of analysis would be performed on the data. However, five companies stated that they would or might perform whole genome sequencing (WGS), which results in a large amount of data and therefore increases the likelihood of discovering incidental findings.[51]

To return findings, researchers must be able to recontact participants. Thus, company policy documents were reviewed for details regarding data identifiability and statements about contacting participants. To protect the privacy of research participants, information regarding their identity is often separated from genetic and self-reported data. Personal identifiers and contact information can remain linked to genetic data through a code or pseudonym, making this data coded. If direct identifiers and associated pseudonyms are hidden from researchers, data may be referred to as de-identified.[10] The method that affords the highest level of privacy is anonymization. Data is anonymized by erasing direct and indirect identifiers from large datasets. In some jurisdictions, de-identification may refer to the removal of indirect identifiers such as gender or date of birth from a dataset, and anonymization may refer to manipulating or aggregating datasets to prevent re-identification.[64]

In analyzing company policy documents, I found that participant data was most often protected through de-identification, as shown in Table 8 below. Three of the company documents did not specify whether participant data would be coded, de-identified, anonymized, or identifiable. In several consent forms, data was referred to as de-identified but appeared to in fact be coded based on the description of the privacy protection strategy. Eight of the companies that purported to de-identify the genetic data they used for research also stated that they re-contacted participants, indicating that contact information was still connected to genetic and self-

reported data. Overall, 19 of the companies stated that they would recontact consumers. Reasons for recontacting included asking for additional consent for new research projects, sending surveys or questionnaires, or delivering updated test reports to customers. In sum, up to 19 of the companies appear capable of returning findings because they recontact participants and retain identifiers. At least four of the companies may not be able to return findings to individual participants since they anonymize the genetic data they use for research. The feasibility of returning findings is also dependent on cost and time constraints for each research project, although this is not something I was able to study by analyzing company policy documents.

Table 8: Privacy measures used by DTC-GT companies and intention to recontact consumers

	Recontact participants		
Data privacy	**Yes**	**No**	**Total**
Coded	8	0	8
De-identified	8	3	11
Anonymized	0	4	4
Unclear	2	1	3
Total	19	7	26

Management of findings

Canadian and international norms for the return of incidental findings in research settings state that if findings can be anticipated, as in the case of genomic research, this should be explained to participants during the informed consent process (Table 5). Participants should also be informed about the researchers' plan for managing such findings. Eight of the 26 companies I studied mentioned the possibility that findings could be discovered during research (n=5) or while processing the consumer's requested genetic test (n=3). Potential findings were only discussed in research consent documents and informed consent documents and not in privacy policies or terms of service, even for companies that did not appear to have consent forms. All

five companies that mentioned the possibility of discovering individual research results in their consent forms recruited participants on an opt-in basis. One additional company with only a terms of service document posted on their website confirmed by email that they use a tiered consent process and have a plan for the management of findings from research. The terminology used to refer to incidental findings or individual results varied significantly between different companies, as shown in Table 9 below. Several companies used phrases rather than individual terms to refer to potential findings. The company documents that mentioned the possibility of findings from genetic testing (not research) referred to them as "incidental findings" and "variants of uncertain significance."

Table 9: Terminology used to discuss potential findings in DTC-GT company policy documents

Type of document	**Terminology used to describe findings**
Research consent	"any results" "information about your or your biological family (blood relatives) that you did not know" "information about you or your genetic relatives that you do not expect or that makes you uncomfortable, such as potential health risks" "information related to a project that you were not aware of such as discovering your ethnicity is not as you thought or that you are in a risk category for a health condition you were not aware of" "test results and/or recommendations" "inherited diseases"
Informed consent	"incidental findings"(*n*=2) "variants of uncertain significance"

While eight companies mentioned the possibility of discovering findings in their consent documents, only three outlined a plan for the management of findings from research. One additional company confirmed by email that they had a findings management plan. Two other companies outlined plans for the management of incidental findings from testing, not research, and three of the 26 companies had plans to share general study results with participants (Figure 3).

All four companies with a plan for the management of findings from research stated that they may return individual findings to participants, however crucial details regarding their return strategy were missing. For instance, they did not explain how, when and by whom findings would be disclosed to participants, nor did they describe any criteria for findings that would be returned. Only one company indicated that genetic counselling may be provided when returning findings. Participants were not given the opportunity to consent or opt out of receiving potential findings, which is an ethical obligation widely agreed upon by the institutions listed in Table 5. Additionally, participants were not asked for consent to disclose findings to biological relatives who may be impacted by this information, an important consideration in genetic research.[10]

Another notable result is that none of the companies outlined a separate findings management plan for participants who are minors, which is relevant because 21 of the 26 companies provide genetic testing to minors with parental consent, and at least three of these allow minors to participate in research. None of those 21 companies stated that they did not include the data of minors in their research databank, thus it is unclear exactly how many allowed or shared this data for the purpose of research. According to Canadian norms, material incidental findings must be returned to minors if actionable during childhood,[10] an obligation which should be disclosed during the informed consent process to ensure guardians are aware they cannot opt out of receiving such information on behalf of the child.

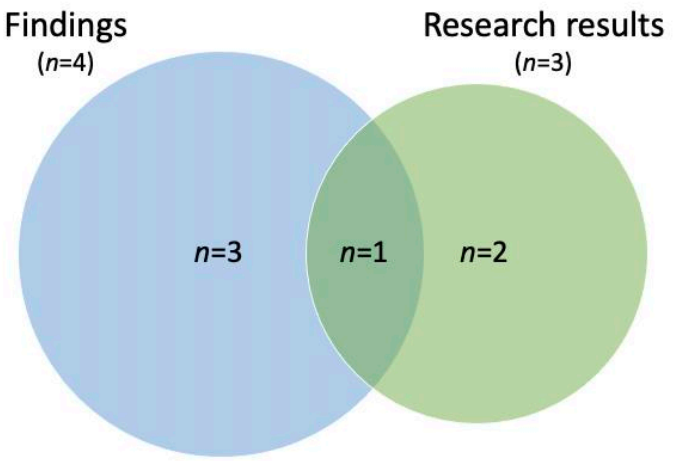

Figure 3: Information returned to participants by six DTC-GT companies conducting research

Ethical oversight

Lastly, I explored whether ethical oversight was associated with greater transparency regarding the issue of findings. Nine of the 26 companies mentioned oversight by a research ethics board (REB) in their policy documents, on their website, or through correspondence. I made the assumption that the remaining companies did not seek approval from an independent REB; the assumption could not be verified because this information is not public knowledge. I found that companies with REBs were indeed more likely than those without REBs to have a plan for the management of individual results and incidental findings; 33% of companies with oversight and only 6% of companies without oversight had a plan (Figure 4). Nonetheless, the majority of companies with an REB did not outline a plan. Thus, the customers of most of the testing firms were not informed of the company's position on returning findings from research regardless of whether the firm had ethics approval. Two of the three companies that had REBs and mentioned the issue of findings in their consent documents had a policy of returning findings

to participants. The other did not articulate their position on returning findings. Although it was unclear for all firms which findings would be returned and how they would be communicated, one company with an REB confirmed by email that genetic counselling would be provided following the disclosure.

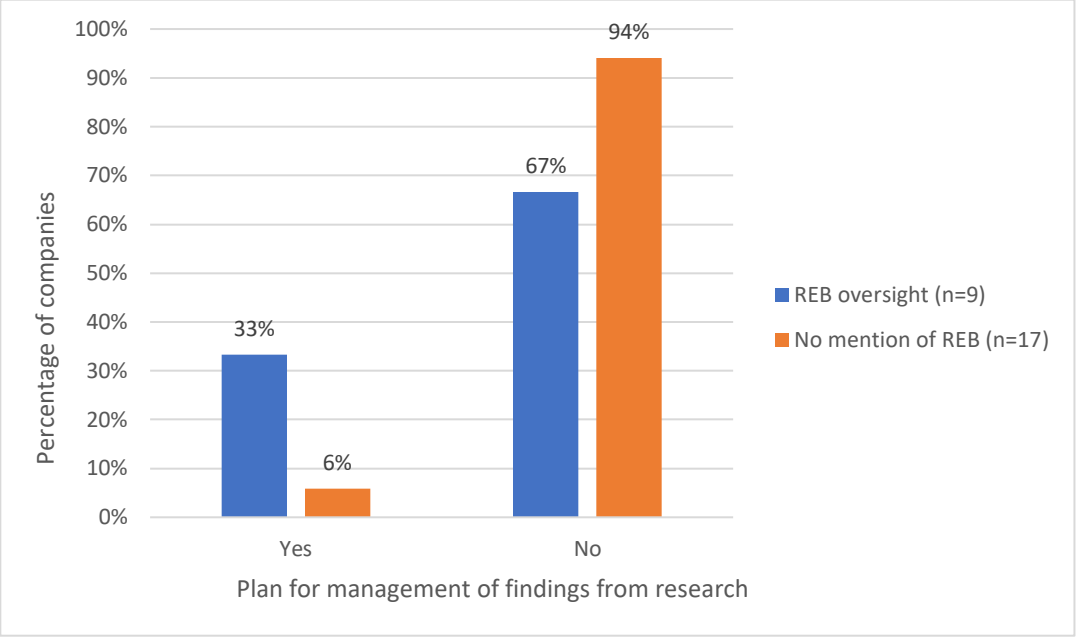

Figure 4: Findings management plans of DTC-GT companies with and without REB oversight

While not all nine companies with ethical oversight addressed the issue of returning findings, they did at least all have separate research consent documents to recruit participants. However, two of these companies could not share their consent documents with me. By comparison, only three (17%) of the 17 companies without REBs had research consent forms, including one company that could not share their document. In a similar vein, firms with REBs (*n*=9) utilized only tiered (33%) or opt-in (67%) methods to obtain research consent, while 12% of companies without REBs used an opt-out strategy and 18% had no consent process at all for research (Figure 5). Although the availability of consent documents and the manner in which

consent is obtained are limited metrics to evaluate a company's research ethics, the results suggest a general trend between ethical oversight and both increased transparency regarding research activities and greater respect for participants' autonomy. Given the small sample size, the results of this section would benefit from replication to validate this finding.

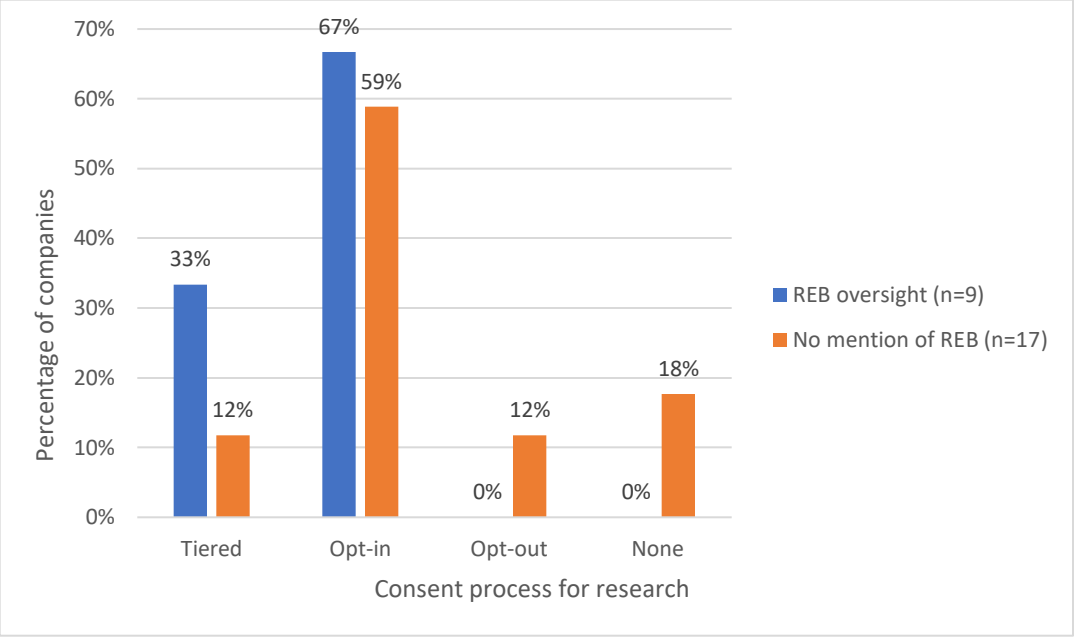

Figure 5: Research consent processes of DTC-GT companies with and without REB oversight

4. Discussion

4.1 Discussion of Results

This project built upon previous studies and commentaries on the research practices of direct-to-consumer genetic testing (DTC-GT) companies. One of the main themes in the literature is whether consumers are duly informed about the research activities and subsequent commercialization that these testing firms plan to engage in using their data.[5,9,33,31,35] As these research projects involve no physical procedures, the biggest risk for participants is a violation of their autonomy and/or their privacy. Informed consent is a recognized standard in research with human participants,[10] including biobanking initiatives.[65,6,17] It involves important ethical procedures such as obtaining initial consent for research participation, communicating any important changes to participants throughout the project and obtaining additional consent when appropriate, and allowing individuals to withdraw from studies if they desire to do so. Although the informed consent process involves multiple steps, consent forms are easier to access and study than actual recruitment, research and data sharing practices, and these documents play a key role in communicating necessary information to prospective participants.[66] In genomic research and other fields involving a high chance of material incidental findings, the initial consent process is also the time when policies for the return of individual results ought to be discussed with participants, and this should normally be reflected in consent forms.[12]

The aim of this thesis project was to study the return of research findings policies of DTC-GT companies, an aspect of ethical research not examined in previous studies of genetic testing firms. In this section, I will situate the results of the study within the larger field of scholarship on DTC-GT research, and I will discuss the implications of the research findings. I

will compare my findings of current research practices in the industry to the normative guidance presented earlier in the Results, and comment on possible ethical consequences of the current practices. I will conclude the chapter with a discussion of the study limitations and of future directions for research in this area. Finally, I will offer some points to consider for genetic testing companies on developing an appropriate strategy for the management of findings from research.

Previous studies of DTC-GT research

Several studies have analyzed the websites and policies of DTC-GT companies to investigate their research activities. The largest such study that appeared in my systematic review of the literature was a 2017 paper by Laestadius *et al*. published in *Genetics in Medicine*, the journal of the American College of Medical Genetics and Genomics. In this study, the authors analyzed the websites and policies of 30 firms performing health and ancestry testing to examine whether DTC-GT companies are complying with international transparency guidelines with regards to privacy, confidentiality and the secondary use of data. In their analysis of these 30 companies, they found that nine disclosed their intent to conduct health-related research and 12 disclosed their intent to conduct ancestry or unspecified research. Out of the nine companies involved in health research, only six indicated they would obtain additional consent, while two others allowed individuals to opt-out of research.[5] In a 2016 study, Niemiec and Howard studied four companies offering whole genome sequencing. They found that two of those companies indicated that they may perform research, neither had a separate research consent document and neither offered consumers the possibility to opt out.[9] In another 2016 publication, Christofides and O'Doherty conducted a study of 86 DTC genetic test websites whose services were available for purchase in Canada, but they only discussed secondary data use for a subset of 29 companies offering health-related testing. They found that five firms used consumer data for research; two

of these used the data with consent, and one used data they considered to be unidentifiable without consent.[31] The most recent publication was a 2018 study by Hazel and Slobogin. The authors looked at the privacy policies of 90 companies and concluded that 24 used data for internal research and development and 16 were involved in third-party research. Of those companies sharing data with third parties, 10 had an opt-in policy and the others shared consumer data by default, with two companies indicating that individuals could opt-out. Nine of the 16 companies discussed the risks of participating in research.[49] None of these studies investigated the issue of returning research results. However, this issue was identified as an area for future research in a 2016 commentary by Tobin *et al.* and was also raised by Adam and Friedman in another commentary published the same year.[7,42]

Transparency of research activities

Examining the consent processes of these private research databases provided helpful context before studying how they manage incidental findings. The amount of information provided to participants during consent (or the lack thereof) is indicative of investigators' transparency practices. Moreover, it would be difficult for companies to inform participants about returning potential findings from research without informing them more generally of their plans to use consumer data for research. Thus, I began the analysis by examining the types of research consent processes of the selected genetic testing companies (Table 7). Over half of the firms examined herein had consent forms for research (n=9) or for testing services (n=7). By providing separate consent documents for research, those nine companies highlighted the fact that they wished to use consumer data for secondary purposes, briefed prospective participants about what this research would entail, and allowed them to make an informed choice regarding participation.

As discussed in the Results (subsection 3.3), not all research consents were available online, and several existing documents could not be retrieved from the companies (Table 6). Some of the policy documents on the company websites referred to additional consent or research documents which did not appear to be publicly available online. These additional research materials may have been provided to participants through client portals, which I did not have access to. When contacting company representatives to inquire about any additional research policies, four stated they were unable to share their consent forms and six did not respond to my request, possibly because of limited personnel or language barriers. This made it difficult to study their research practices.

This problem extends beyond the realm of DTC-GT research. It is not standard for informed consent forms to be made publicly available in research, and until recently it was rare to be able to access them online.[66] This makes it challenging for bioethics scholars and the public to ensure that research involving human subjects and their data is conducted in accordance with accepted ethical principles. In 2019, the United States government made it a requirement to include consent documents in their national clinical trial registry after repeated calls from scholars for more transparency in clinical research to facilitate public scrutiny and ultimately the improvement of consent procedures.[67,66,68] Publishing consent forms is not required for other types of studies involving human participants such as feasibility studies, observational studies or non-medical research. On a positive note, my results show that genetic testing companies have already begun to share their research consent documents online even though they are not required to. Of the companies investigated in this study, seven had a research consent form publicly available on their website (Table 6). It would be beneficial for other companies to

follow suit to allow for public scrutiny and to promote consensus policy development within the industry.

The majority (*n*=16) of companies asked consumers to opt in to participating in research, while two automatically enrolled participants but gave them an opportunity to opt out, and five allowed subjects to separately consent to individual studies. Only a few (*n*=3) companies used the data of all consumers for research with no possibility of opting out. However, it should be noted that two firms gave consumers the choice to contribute their data or not to research collaborations with third parties but did not allow them to opt out of research conducted solely by the testing company. Additionally, another two firms requested consumers' consent for certain studies but did not allow them to opt out of research conducted using de-identified and aggregate datasets.

That most companies obtained separate consent either to store consumer data in their research databank or to use this data for individual studies is in line with established principles for ethical research. The standard in research with human participants is to obtain informed research consent before enrolment in a study. Since DTC-GT companies have created research databanks, it is particularly appropriate to discuss their practices in relation to the standards for databanks or biobanks. Biobanks generally recruit participants on an opt-in basis. Patients or members of the public may opt to contribute their samples and data to a particular repository after being prompted by their physician or coming across a recruitment notice.[6,17] While early biobanks favoured study-specific consent, there is now a trend towards broad consent as well as alternative models including tiered or dynamic consent, in which donors may consent to specific categories of research.[65] Thus, it may be most appropriate for genetic testing firms to recruit research participants on an opt-in basis, and to obtain study-specific or tiered consent if possible.

Importantly, participant preferences are in agreement with these consent standards. DTC-GT consumers have expressed that they want to be asked for permission to use their data for research activities, with numerous consumers preferring to be informed every time the company wishes to use or share their data.[69]

Types of potential findings

While many of the companies examined provided basic information about the risks and benefits of participating in research, the majority did not explain what kind of findings may be incidentally uncovered. Genomic research can reveal a wide range of information with personal significance. The types of findings that may be discovered in a particular study are dependent on the type of analysis that is performed. For instance, when examining DNA sequencing data, researchers may detect a genetic disorder, such as Wilson's disease, or a variant associated with a higher risk of multifactorial or polygenic diseases, such as heart disease or cancer. Chromosome analysis, another technique, may uncover autosomal or sex chromosome aneuploidies. In family studies, genetic analysis may reveal misattributed paternity.

The company policy documents I examined provided very few details, if any, about which regions of the genome would be investigated in their studies or what type of analysis would be conducted with the genetic data collected from participants, making it difficult to predict the range of possible findings that could be uncovered. The terminology used by companies in their policy documents was somewhat vague, with some companies specifying that analysis could reveal inherited disease, a health risk or the participant's ethnicity (Table 9). Five firms indicated that they may perform whole genome sequencing, which involves a high likelihood of discovering incidental findings.[51] Despite this, three of those five companies do not discuss the possibility of findings in their policy documents.

To better understand what analysis may be performed in their research, we can turn to the methods these companies use for their test products, which is sometimes described in their policy documents or on their websites. While some DTC companies offer whole genome or exome sequencing services, many genetic testing companies instead use genotyping techniques to produce health, ancestry and lifestyle DNA reports for their customers.[1] Unlike sequencing, which determines the exact sequence of DNA ranging in size from a short fragment to the entire genome, genotyping is used to investigate certain pre-determined variants of interest. Because genotyping generates less data than large-scale sequencing, it is less likely to produce incidental findings. However, since genetic testing companies possess consumer samples, firms that primarily offer genotyping services can still perform sequencing or other genome analysis techniques to generate more data for research purposes. For example, 23andMe's tests are based on genotyping techniques,[70] but they state that they may perform further analysis such as WGS in their research.[71] This can be performed only a limited number of times before the sample is depleted, but once the additional analysis is completed, the resulting data can be stored and re-investigated for any number of studies. Moreover, if analysis is outsourced to other laboratories for third-party research, these facilities may already be equipped to identify certain variants that should be reported to participants. The American College of Medical Genetics and Genomics (ACMG) recommends that laboratories conducting large-scale genetic sequencing actively look for and report variants in 73 genes underlying disease phenotypes.[72] This recommendation is intended for clinical laboratories; the PCSBI, an advisory panel to the American government, stresses that researchers do not have an ethical duty to actively look for secondary findings as the primary purpose of research is to produce generalizable knowledge.[62]

In some cases, incidental findings and individual results can help inform disease treatment or prevention, and reproductive, career, or lifestyle decisions. Other findings may have limited utility and participants may prefer not to receive them as they may cause unnecessary anxiety.[62] To avoid returning results with uncertain significance and limit the costs and labour associated with the return of findings, it is important for researchers to establish clear criteria to evaluate whether to disclose a discovered finding.[60,63] Research ethics boards can support investigators in making these decisions.

Plans for the management of findings from research

Overall, less than a third (8/26) of companies addressed the possibility of findings in their publicly available policy documents. Five out of the nine research consent forms discussed potential findings from research and three out of the seven informed consent forms addressed potential results outside of the test scope. Even though some companies only discussed their research activities in their privacy policies or terms of service, and did not appear to have developed consent documents, their available policies did not mention the possibility of discovering findings. The fact that this prospect was not disclosed in privacy policies or terms of service is not altogether surprising as the primary purpose of these types of documents is not to provide details of company research activities. This supports the notion that participants ought to be recruited through a separate consent process,[5,15,9,35,7] so that researchers can highlight the benefits and risks of participating in research and alert participants about what kind of information could be uncovered and disclosed to them.

Three companies indicated in their consent forms that they may return findings to participants. The risk section of Ancestry's research consent document stated that "if [they] were to provide [participants] with information about [their] Genetic Data," they may learn

unexpected information "such as potential health risks." This suggests that they may share individual research results or incidental findings with participants.

Living DNA indicated in their research consent form that all participants would have access to their "raw genetic data file" through the company's customer platform. They also stated that they would share "the progress of any research and findings" with participants by email. When discussing the risks of research, they stated that participants may learn "information related to a project that [they] were not aware of, such as discovering [their] ethnicity [was] not as [they] thought or that [they were] in a risk category for a health condition [they] were not aware of." This wording suggests that Living DNA may return individual research results but not incidental findings.

When describing what analysis their research may involve, Viome stated that they may perform "personal genetic analysis to understand possible connections between [participants'] genes and [their] health, wellness, and lifestyle" but would not "sequence [participants'] genome or look for inherited diseases." It is possible the genetic analysis referred to here is genotyping. They also indicated that they may perform gene expression analysis. From this language, it seems that Viome does not intentionally search for disease-causing variants. However, when discussing the benefits or participating in research, they explain that their research may result in discoveries and new products, and state that they "may or may not provide [participants] with the test results and/or recommendations." They add that this would be explained further in separate recruitment materials. This suggests that Viome may share individual research results with participants, or individual results of new tests that are developed through their research.

One additional company, Sano Genetics, confirmed by email that they return results to participants wherever possible. They indicated that findings are managed differently for each

research project, based on the context of the research and whether their collaborators or ethics board for that project require them to offer additional support such as genetic counselling. They have separate consent forms specific to each study they conduct.

Genetic testing companies may often have different policies when producing in-house research and when collaborating with third parties. For instance, academic researchers are subject to institutional ethics review and may be required to return certain findings to participants. Indeed, three companies I examined appeared to have separate research consents or additional recruitment materials for specific projects, possibly to meet the standards of their different research partners. I could not examine whether or how their return plans differed as company representatives were unable to share these additional recruitment documents.

Interestingly, unlike the four companies discussed above, 23andMe indicated in their research consent form that they have a no-return policy for individual research results. This policy is clearly stated in the benefits section of the document: "we will not give you individual results about your genetics or health risks that we learn through 23andMe Research." However, it is noted that they may share general research results with participants. Although it is unclear why this information was located in the benefits section, it may have been to dispel any therapeutic misconception.

Given the limited information that is provided by genetic testing firms about their research activities, it may be challenging for participants to understand the likelihood or risk of discovering incidental findings or individual results, what kind of information could be revealed, and the implications for them and their biological relatives. Since all the companies that were studied neglect to collect additional consent for the return of findings, it may also be impossible for participants to express their preferences about which types of information they would like to

receive or would not like to receive. This problem is not unique to the realm of DTC research. It is common for biobanks to lack policies for the return of findings, however organizations and regulatory bodies have attempted to resolve this by developing guidelines for appropriately managing findings in a biobanking context.[4]

How do these practices compare to return of results guidelines?

Overall, the industry research practices do not consistently adhere to Canadian and international guidelines for the return of findings from genomic research. There is consensus between nearly all organizations in Table 5 that researchers should explain to participants, during initial consent procedures, what information may be revealed about them during research and whether or not these findings will be communicated to them. Additionally, the PCSBI recommends that DTC-GT firms inform consumers of incidental or secondary findings that may arise from a test and clearly state whether these will be returned or not. This should be addressed before the testing procedure to enable consumers to make responsible and informed choices regarding DTC services.[62,73] The majority (21/26, or 81%) of companies did not mention in their recruitment documents that significant information may be discovered in the course of research, and the documents that did mention this as a possibility were vague when describing the type of result that could be discovered (Table 9). An even larger number (23/26, or 88%) of companies did not articulate their position on the return of findings. While biobanks and data repositories may not be ethically warranted to return material findings from research, their no-return policy should be highlighted during consent procedures (Table 5).

The companies that indicated they may return individual-level results to participants did not specify how they would choose what information to return. While some genetic biobanks, such as the Personal Genome Project,[46] choose to share all individual-level data with participants

as a matter of reciprocity,[74] this data could be challenging for participants to interpret. Unless researchers plan to share all raw data with participants, they should specify the standards by which findings will be evaluated prior to being disclosed. The most common criteria outlined in the return of results guidelines were significance, actionability, and validity (Table 3). In some cases, it may be difficult to assess the clinical utility or personal significance of a finding,[12] particularly since DTC providers may not have much knowledge of participants' circumstances. The list of secondary findings published by the ACMG can be referenced as a guide to determine which gene variants should be reported.[72] Researchers should also ensure that findings returned are actionable, meaning that the risk to the participant's welfare can be mitigated trough treatment, prevention or lifestyle decisions.[12] To ensure clinical validity, DTC-GT firms may need to have results independently validated by a clinical laboratory. As this represents an additional cost, researchers may wish to establish the significance and actionability of the result before proceeding to validation.[60]

Although 21 companies allowed the purchase of genetic testing services for minors and at least three of these allowed minors to contribute to their research databases, none articulated whether findings would be handled differently for individuals under the age of majority. This could be problematic in certain jurisdictions. In Canada, guardians of minors must, by law, exercise their authority in the best interests of the child, and this has been interpreted in the TCPS 2 to mean that parents cannot refuse any findings that are actionable during childhood.[10] This obligation should be clearly stated in consent documents so that guardians are aware they must accept to receive such information on behalf of the child if there are preventative or therapeutic interventions available during childhood. Refusal of this information could be considered medical neglect.[60] This norm is not unique to the Canadian context. It is echoed in

guidelines developed by the European Society of Human Genetics for pediatric biobanks, which stipulate that parents should be notified of information regarding preventable or treatable early-onset disease even if parents do not wish to receive findings concerning their child.[75,76] It is important to note that unless treatment must be initiated during childhood to prevent harm to the participant, information regarding adult-onset conditions generally should not be returned, unless it could have important implications for their adult relatives. The reason for this is to avoid causing psycho-social harms and to allow the child to decide in the future whether they wish to know this information about themselves.[60,77]

The company documents examined did not clearly outline the communication modalities chosen for the return of findings. It was unclear who was designated to communicate significant information to participants, whether that be a researcher, a genetic counsellor, or another member of the research team or company. In several cases, it was also unclear how participants would be contacted. As the DTC-GT companies studied were primarily web-based, it is likely that findings would be delivered remotely, perhaps by email, through an online portal, or by phone or video call. Some normative guidelines suggest that access to genetic counselling should be provided when returning findings if it is possible and appropriate (Table 5). This exercise can help participants to understand the clinical significance of the information, available interventions, and the implications for their biological relatives.[60] Only one company, Sano Genetics, confirmed that genetic counselling would be provided when returning findings. Although some guidance suggests that genetic counselling is not always necessary, the participant should still be explained the meaning and implications of the result in all cases.[55,56,58]

Finally, the organizations in Table 5 agreed that researchers must obtain the consent of participants for the return of findings and respect their choice to refuse this information. Consent

should be requested from participants after they have been informed of what information may be revealed and how researchers plan to manage these findings. However, none of the company documents examined herein provided an option for participants to consent to (or refuse) the return of significant information discovered during research.

Potential consequences of DTC-GT company research practices

This failure to collect informed consent and to clearly outline the risks and benefits of participating in research, including the possibility of incidental findings, contributes to the blurred relationship between company, researcher and consumer-participant.[5,9,78] When it comes to the disclosure of findings, the responsibilities of test providers and researchers towards participants are unclear. As discussed already, the possibility of discovering findings is rarely discussed with clarity in DTC-GT consent forms. In the absence of clear information, participants are left to their own expectations regarding the management of findings, which may not align with researchers' intentions or plans. Participants may expect to receive significant findings about their health or identity if they participate in research, particularly if they ordered a test to learn more about themselves.[4] A 2017 survey of 1,648 DTC-GT consumers reported that the main motivators for purchasing DTC genetic testing services were to learn about one's ancestry, personal traits, and disease risks.[79] Several other surveys, polls and studies of online forums have yielded similar results regarding consumer motivations.[32,31,80,81,69] Thus, many consumers that choose to participate in research may wish or expect to receive any findings about their health or identity.

On the other hand, some participants may receive surprising or disturbing findings without expecting them due to the lack of a separate consent process for the disclosure of individual results. An individual who has ordered a genetic test solely to learn about their

ancestry or for genealogy purposes may not expect or want to receive information about their health risks, even if they have agreed to the use of their genetic data for health-related research. In this case, returning findings without consent is a violation of participants' right not to know.[62] The unexpected return of information may also cause distress to participants about their personal health or identity or about the prospect of having to deliver bad news to their family members.[44]

Regardless of consumer expectations, neglecting to explain to potential participants the possibility of findings prior to recruitment prevents them from making a fully informed choice to participate in research. Previous studies have shown that DTC-GT customers desire better transparency about data usage, easier readability of policy documents, and more information regarding the risks and limitations of genetic testing.[35,82,31,69] This lack of transparency and missing element of informed consent may undermine public trust in genetic testing companies and their research partners as well as the genomic research enterprise more generally. As others have warned, a loss of trust in DTC research endeavours could potentially hinder subject recruitment for genetic research in general, not only in a DTC setting.[16,5,9,23,27,28] For genetic testing firms, this could lead to fewer research collaborations, which may be critical for their viability as a business.[7,14]

Is feasibility the issue?

It is unclear why the issue of findings is often not addressed in DTC-GT research policies. One reason could be that returning individual results is not feasible. It is likely that companies are able to recontact participants as most of them appear to retain personal identifiers to allow them to recontact participants for research surveys. It is more plausible that companies have no-return policies because of time or resource constraints or because they are hesitant to return unvalidated findings. Some company documents indicated that third-party researchers

would not have access to personal identifiers and contact information of their participants. However, in the event that incidental findings are discovered during their analysis, third-party researchers could alert the original DTC company in order to ensure this information is conveyed to the participant.

It may be challenging for genetic testing companies managing large research databases, some with millions of participants, to return findings due to resource constraints relating to their business model. As discussed above, the creation of DTC-GT research databases is a profit-generating venture, and the return of validated findings to participants may not be profitable. Companies may not wish to divert funds to independently validate findings that are discovered, and they may not have the expertise and infrastructure to appropriately communicate these to individual participants. DTC-GT companies may also not have the resources to provide genetic counselling to participants receiving findings. However, they should always explain the possibility of discovering findings to participants during the research consent process, and outline their management plan for findings, including no-return policies.

Possible explanations for omission of plans

There are several possible reasons why genetic testing companies are not consistently adhering to the existing guidelines for the return of results from research. For instance, this may stem from a lack of independent ethical oversight. Genetic testing firms may not be familiar with the guidelines for the management of incidental findings and individual results, which state that participants should be informed of plans to return or not return findings. However, I found that several companies that declared that their research was supervised by an IRB still lacked transparent plans for the management of findings (Figure 4). Companies involved in third-party research collaborations could have return of results policies for those projects but not for in-

house research, thus relying on the policies of their institutional or industry partners to abide by regulations or guidelines that are applicable to their research activities. Further research may be needed to investigate these hypotheses.

More speculatively, the lack of transparent research plans and of research-specific consent processes may also be explained by financial incentives related to recruitment.[5] Neglecting to obtain separate consent for research and remaining vague about the possibility of returning incidental findings may allow DTC-GT companies to recruit more participants for research. A 2021 survey of 415 individuals living in Canada found that survey participants who had considered DTC genetic testing but had ultimately chosen not to purchase a test were concerned about the company sharing their data with others, including researchers.[31] Not all individuals who consider DTC-GT closely read the companies' policies and terms of service, and many are unaware that their data may be used for secondary purposes. A 2020 survey of 23andMe users found that 41% of respondents did not know that the company could use and share their data for research and to develop drugs and diagnostic tests at the time they took the test. Importantly, 7% of respondents stated that they would not have taken the test if they had known this, and 16% stated they were unsure.[69] Genetic testing companies may be aware that informing potential customers about data sharing and privacy risks can deter individuals from purchasing a test or opting in to research. There is a financial incentive to continue accumulating consumer data for research since several companies have forged profitable research partnerships with pharmaceutical and biotech companies using this data, and larger datasets are more attractive.[8,16,14]

Moreover, the existing norms may not adequately meet the needs of the DTC-GT research context, as they are often developed for academia or the public sector. Although many

return of results guidelines provide guidance for genetic researchers and biobanks, most do not offer recommendations specific to the DTC setting (Table 4). While the PSCBI does not address DTC-GT research, they do argue that genetic testing companies should inform customers of potential incidental findings from testing.[62] The issue of returning individual results is not directly discussed in the *Privacy Best Practices for Consumer Genetic Testing Services*, although the document does refer to the *Common Rule*, which outlines guidance on this subject.

Companies conducting research with the data of customers in multiple jurisdictions may not be aware of all the regulations they are subject to, and these norms may contradict each other. DTC-GT companies are not subject to federal human subjects research regulations in the United States unless they conduct publicly funded research using identifiable data,[13] or data that could be re-identified, such as research involving WGS.[43] In Canada, the regulatory landscape surrounding human research is complex. Publicly funded research must adhere to guidelines outlined in the TCPS 2, and independent REBs contracted by private researchers may also refer to this policy as it has created an ethical standard for research in Canada. Additionally, several provinces require research with human participants to be supervised by an REB, regardless of whether it is conducted in the public sector. For example, article 20 of the *Civil Code of Québec* requires any research that could "interfere with the integrity of the person"[83] to be approved by a research ethics committee. As psychosocial integrity relates to an individual's personal privacy, it can be interpreted that this article of the CCQ applies to research involving the secondary use of identifiable biological specimens or data.[84] Likewise, in Newfoundland and Labrador, the *Health Research Ethics Authority Act* states that health research must be approved by an REB that applies standards outlined in the Tri-Council Policy Statement.[85] As the TCPS 2 is the predominant national policy for research ethics in Canada, research supervised by Canadian

research ethics boards should address the issue of material incidental findings during consent procedures. Since many DTC-GT companies examined herein are headquartered outside of Canada, it is important to note that researchers from other countries that have approval from an IRB in their country may recruit participants for genomic research in Canada without the additional approval of a Canadian REB, unless they are collaborating with a Canadian institution.[45] Additionally, there are potential ethical issues for companies conducting pediatric research with Canadian participants, as they are required to return findings that are actionable during childhood.[60] Moreover, DTC-GT companies may also face administrative or legal repercussions in other countries for ignoring local return of results norms.[86,87]

4.2 Study Limitations

The main limitations of this study were related to the method of selecting companies and of retrieving internal policy documents. As there is no comprehensive directory of private genetic testing companies operating worldwide, I searched both the academic literature and the internet for names of companies. This was the same strategy used in a 2017 study looking at DTC-GT companies involved in research.[5] I did not review all the results of the literature and internet searches as I observed saturation after reviewing several pages of results. The company selection was limited to companies with an online presence for convenience, though this was also a useful proxy to filter out spurious businesses. Naturally, the selection criteria chosen for the project also limited the number of companies that were studied, but these were aligned with the objective of investigating specifically companies that were involved in research with the data of Canadian customers (Table 1). To build on the results of this study, future research could expand the analysis to companies not currently serving Canadians and compare the return of results policies of companies operating in different jurisdictions.

More importantly, the unavailability of company documents hindered my analysis of company policies for the return of findings. As discussed earlier in the Discussion (subsection 4.1), I was not able to retrieve all existing research-related documents from the selected companies. This incomplete data makes it difficult to accurately assess the participant recruitment practices and research policies of genetic testing companies. Since most of the available company documents lacked information regarding their policies for returning incidental findings and individual results, it was difficult to draw conclusions about how they manage findings discovered during research. Low retrievability of documents and insufficient detail are two of the common limitations of document analysis as a qualitative research method.[52] However, the efficiency and cost-effectiveness of this method make it very suitable for exploratory research. In time of writing, this is the first study investigating the return of findings policies of DTC-GT companies involved in scientific research.

4.3 Points to Consider for the DTC-GT Industry

It is encouraging that several of the genetic testing firms studied had a research consent or general consent document publicly available and that others were responsive to requests for recruitment materials. This demonstrates that they are making an effort to respect research ethics standards and to be more transparent about their research policies. There have been repeated calls from bioethicists and research institutions for the direct-to-consumer genetic testing industry to establish a code of conduct or best practice guidelines to improve current research practices and promote adherence to established ethical standards.[5,9,29,27] Attempts at self-regulation have already been made: in 2018, several leading genetic testing companies collaborated with the Future of Privacy Forum to develop the *Privacy Best Practices for Consumer Genetic Testing Services* with the aim of protecting consumer privacy.[30] These

guidelines could be revised to include further guidance on the secondary use of consumer data for research, and to outline best practices for the management of incidental findings or individual research results. In that view, I have devised a brief list of points to consider for direct-to-consumer genetic testing companies involved in research using consumer data (Table 10).

Table 10: Points to consider for the ethical management of findings from research conducted by direct-to-consumer genetic testing companies

Points to consider on the management of findings from DTC-GT research

• There is consensus in the normative guidance that researchers should prepare a plan for the return of research results and incidental findings and present it to their REBs.
• This plan should be explained to potential participants. In the interest of transparency, the plan may be made available to the public on company websites, along with research consent documents.
• Investigators should provide the option for adult participants to receive analytically valid, clinically significant, and actionable findings, unless impracticable or impossible.
• For pediatric research with Canadian participants, investigators should inform guardians of minors that they must receive findings actionable during childhood.
• Initial consent procedures are an appropriate stage at which to inform participants of potential findings and manage expectations about the return of individual-level results. The following elements may be included in the research consent to achieve this:
  o The types of information that may be revealed during research;
  o The potential implications for the participant and their biological relatives;
  o The research team's policy for returning findings;
  o The planned communication modalities for the return of findings; and,
  o The support available to participants receiving significant findings, such as genetic counselling.

5. Conclusion

This thesis project aimed to investigate how direct-to-consumer genetic testing companies approach the return of incidental findings and individual-level research results in their research endeavours. To meet my first objective, which was to examine the current research practices of the DTC-GT industry, I analyzed the consent documents and policies of 26 web-based companies offering genetic testing services to Canadian consumers. Analysis of these documents revealed that less than a third of the firms informed prospective participants that their research may reveal significant individual-level information. Further, only four companies appeared to have a plan for the return of findings. It was unclear how and when any important findings would be communicated to participants, and whether the results would be evaluated for clinical validity and actionability. Thus, the document analysis results indicate that DTC-GT firms involved in research rarely inform prospective participants of their policies for the return of individual-level findings, addressing Objective 1.

To satisfy the second objective, I compared these research practices to normative guidance from 11 international, Canadian, and American organizations. While this guidance did differ for certain contexts such as biobanking and pediatric research, I found that there is a consensus between major organizations regarding how to address potential findings in genomic research. In particular, the existing guidance consistently stated that regardless of whether researchers plan to return individual-level findings, they should inform participants of their policy for the management of findings and only return findings with their consent. The comparative analysis of the company documents and norms indicated that genetic testing companies do not consistently adhere to established guidelines for the return of findings from

research, as many do not articulate their position of the return of findings in their policies nor request participant consent for disclosing this information.

The final objective of the study was to address the gaps identified in the policy documents of direct-to-consumer genetic testing companies by providing guidance for the management of findings in this particular context. I proposed several points to consider informed by the academic literature, the perspectives of DTC-GT firms and their consumers, and the existing normative guidance on the return of incidental findings and individual research results. The aim of these suggestions is to offer guidance to DTC-GT companies on developing policies for the management of findings from research.

The results of this study have important implications. It is crucial for private genetic testing companies conducting research to have detailed plans for the management of findings that may be revealed in their analysis, and to disclose these policies to prospective research participants. Currently, these companies are not consistently informing consumers about this potential outcome of participating in research. This may amplify the therapeutic misconception, particularly if individuals are motivated to donate their data for research to receive results about their health or identity. In all, this lack of transparency could have far-reaching consequences by undermining the public's trust in genomic research and hindering future initiatives.

It would be a very interesting avenue for future research in this area to conduct a survey or series of interviews to ask company representatives directed questions about their return of results policy for research participants. These studies may have a low response rate due to the limited personnel responding to requests, especially since these representatives would need to be familiar with their company's research policies. Nonetheless, they may generate further insights

into how private genetic testing providers manage the return of findings from research and the reasoning behind their current policies.

This study helped to clarify how direct-to-consumer genetic testing companies manage research findings and identified gaps between the current practices and the expectations outlined in ethical norms. This knowledge contributes to efforts to improve the research practices of DTC-GT providers, such that all Canadians who choose to participate in genetic research may benefit from existing guidance on the return of findings in genetic research. The results of this study are useful for developing updated guidelines for the management of individual-level findings with a particular consideration for the direct-to-consumer context. They may also serve to guide the DTC-GT industry in developing revised best practices for conducting research with consumer data that include guidelines for the return of findings. This exercise could help to promote adherence to ethical research standards in the industry.

With the support of their large consumer bases, private genetic testing companies have the potential to further genomic research and aid in the development of novel diagnostic and therapeutic techniques. However, this work should be guided by established standards for the ethical conduct of research with humans and their data. Building on previous research on this topic, this exploratory study has investigated the return of results practices of DTC-GT businesses involved in research and suggested how companies can improve these practices by adjusting their strategies for the management of findings. In time of writing, this study is the first to examine how genetic testing companies handle this important issue and to identify gaps between current company practices and established norms for the return of findings in genomic research.

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Appendix A: Document Analysis Codebook

General company data

- Name
  - If multiple names: [platform] by [company] ([parent company])
- HQ location
  - Country
- Type(s) of DNA test(s) offered
  - Health
  - Ancestry
  - Lifestyle
- Physician approval required to order test
  - Y/N

Research details

- Conduct research with Canadians
  - Y/N/U
- Conduct pediatric research (with Canadian minors)
  - Y/N/U
- Research consent process
  - Tiered (T)
  - Opt-In (OI)
  - Opt-Out (OO)
  - Not Optional (NO)

Document analysis

- Type of document
  - Research consent (RC)
  - General informed consent for provision of services (IC)
  - Privacy policy (PP)
  - Terms of service (TOS)
- Type of analysis used in study
  - Eg GWAS
  - Unspecified (U)
- Does company re-contact participants
  - Y/N
  - For future research (new surveys, additional consent)
  - Other purposes
- Storage of genetic data & personal information for research
  - Anonymized (Anon)
  - Deidentified (DeID)
  - Coded (Cod)
- Mention possibility of discovering individual research findings
  - Y/N
- Terminology used for findings
  - Quoted from text
- Plan for management of findings outlined or mentioned in document
  - Y/N

- Findings returned to participants (individual findings from research)
    - Y/N/U
- General, non-identifiable results returned to participants
    - Y/N/U
- Criteria for returning findings
    - E.g. significant implications, actionable, clinically/analytically valid
    - Unspecified (U)
- Consent requested for return of individual findings
    - Y/N
- Can participants choose which types of findings they wish to receive (tiered consent)
    - Y/N
- Consent requested to share findings with biological relatives
    - Y/N
- Who is responsible for returning findings
    - Position (e.g. researcher/investigator, genetic counselor, participant's physician/HCP etc.)
    - Unspecified (U)
- How are findings returned
    - E.g. phone call, email, meeting
    - Unspecified (U)
- When are findings returned
    - E.g. when discovered, during follow-up
    - Unspecified (U)
- Genetic counselling provided when communicating findings
    - Y/N
- Provisions for research participants who are minors (outlined in document)
    - Y/N
    - N/A (i.e. company does not conduct pediatric research)
    - Return
    - Do not return
    - Criteria (e.g. actionable during childhood)
    - Re-contact for consent for results not actionable during childhood
- Mention of REB/IRB in consent document
    - Y/N
- Reporting obligations stated in consent document (e.g. child welfare)
    - Y/N
- Statement that providing diagnosis is not the purpose of the research database or study
    - Y/N

Appendix B: Research Policy Documents Retrieved from Selected DTC-GT Companies

Company	Research Consent	Informed Consent	Privacy Policy	Terms of Service
23andMe[1]	x			
24Genetics		x		
Ancestry	x			
Atlas Biomed				x
Circle (Prenetics)		x		
Color Health		x		
FamilyTreeDNA (Gene by Gene)			x	
Fitness Genes	x			
GenePlanet				x
Helix	x			
Inagene		x		
InsideTracker by Segterra	x			
Invitae		x		
Living DNA	x			
Mental Health Map by Genomind			x	
Muhdo				x
MyHeritage	x			
Nebula Genomics			x	
Pillcheck by GeneYouIn		x		
Rightangled Ltd			x	x
Sano Genetics				x
Sequencing.com			x	
Silverberry Genomix	x			
Stripe2be (Dante Labs)				x
tellmeGen (Genelink)		x		
Viome	x			
Vitagene	x			

[1] Used as a comparator but not included in the results as they do not allow Canadian consumers to participate in research.