Sequencing Peek-a-Boo: Uncovering a Baby's Future Using Newborn Screening Ethical Considerations for Genetic Counsellors

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Abstract

Newborn screening (NBS) is a public health strategy that identifies asymptomatic newborns at risk for developing pre-selected health conditions. NBS programs enable early intervention and treatment, improving newborns' quality of life and even saving lives. The decrease in cost and technological development of whole genome sequencing (WGS) created a surge of interest in its integration into NBS programs. WGS could expand the scope of screening conditions beyond those with well-established clinical management and treatment available.

WGS-NBS programs, however, raise new ethical issues that impact the practice of healthcare providers who have direct contact with patients and families. In particular, genetic counsellors (GCs) are involved in pre-and post- counselling of genetic screening. They guide patients and their families to make informed medical and personal decisions. GCs will play an essential role in WGS-NBS should it become a standard of care. However, there is a lack of literature on how their ethical duties are challenged by WGS-NBS in Canada.

This study examines how the duties of GCs fare with the ethical challenges WGS-NBS poses. First, a literature review followed by a thematic analysis identifies the ethical concerns for GCs: 1) the concerns in managing, interpreting, and communicating WGS results; 2) the impact on the informed consent process; 3) the potential psychosocial and long-term risks to the family and child 4) practical challenges and 5) equity, diversity, inclusion, and accessibility issues. Subsequently, a policy analysis examines how GCs' duties toward their patients, themselves, their colleagues, and society fare with WGS-NBS. Finally, this study proposes points to consider for GCs' clinical practice, such as the development of new consent practices, the need for long-term counselling

and educational tool for parents, the development of new guidelines for GCs through communities of practice and the need to increase accessibility to genetic counselling in Canada.

Résumé

Le dépistage néonatal (DNN) est une stratégie de santé publique qui permet d'identifier les nouveau-nés asymptomatiques susceptibles de développer certaines maladies. Les programmes de dépistage néonatal sont offerts dans la plupart des pays et ont amplement bénéficié aux nouveau-nés et à leurs familles, car la détection précoce des maladies permet de mettre en place des traitements et des plans d'action qui améliorent la qualité de vie et même sauvent la vie des enfants. La baisse des coûts et l'évolution technologique du séquençage du génome entier (WGS) ont suscité un regain d'intérêt pour sa mise en œuvre dans les programmes de DNN. Le WGS pourrait élargir le nombre des conditions dépistés au-delà de celles dont il existe une prise en charge clinique bien établie et un traitement disponible.

L'intégration du WGS dans les programmes de DNN soulève de nouvelles questions éthiques, notamment l'impact sur la pratique des prestataires de soins de santé qui sont en contact direct avec les patients et familles. En particulier, les conseillers en génétique (CGs) sont impliqués dans le conseil pré et post dépistage génétique. Ils assistent les patients et leurs familles à prendre des décisions médicales et personnelles. On s'attend à ce qu'ils jouent un rôle important dans le cadre du WGS-DNN. Ceci dit, il existe aujourd'hui un manque de compréhension adéquate sur la manière dont la pratique des conseillers en génétique sera impactée par l'utilisation du WGS-DNN au Canada.

Cette étude examine les obligations des CGs au Canada dans le contexte du WGS-DNN, d'un point de vue éthique. Tout d'abord, une revue de la littérature suivie d'une analyse thématique permet d'identifier les considérations éthiques pour les CGs: 1) les défis liés à la gestion et à la communication des résultats du WGS, 2) l'impact sur le processus de consentement éclairé, 3) les

risques psychosociaux potentiels pour les familles et enfants 4) les défis pratiques et 5) les questions d'équité, de diversité, d'inclusion et d'accessibilité. Ensuite, une analyse normative examine les devoirs éthiques des CGs vers leurs patients, vers eux-mêmes, vers leurs collègues et enfin, envers la société. Par la suite, cette étude identifie les points à considérer pour les CGs dans le cas du WGS-DNN, entre autres: l'élaboration de nouvelles pratiques de consentement pour le DNN, la nécessité d'un conseil à long terme et d'outils éducatifs pour les parents, l'élaboration de nouvelles directives et normes de pratiques pour les CGs par des communautés de pratique et de la nécessité d'accroître l'accessibilité au conseil génétique au Canada.

Land Acknowledgement

I would like to acknowledge that I work and live in Tiohtià:ke/Montréal, which is the traditional and unceded territory of various Indigenous Nations, including the Kanien'kehá:ka (Mohawk). I recognize and honor the Indigenous peoples whose presence marks this territory.

My thesis explores ethical and policy issues in pediatrics and aims to promote patient-centered and accessible health care to children. In reflection of these themes, I would like to bring awareness to Bear Witness Day, on May 10th, recognizing Jordan's Principle-a principle to ensure equity in services provided to First Nation children: https://fncaringsociety.com/bear-witness-day .

Illustration by local Tiohtià:ke artist: Annick Gaudreault

Source: Montréal en action (https://montrealenaction.com/en/land-acknowledgment)

Contribution of Authors

Ana Eliza Bonilha is the sole author of this MSc thesis. She completed this work under the supervision and financial support of Prof. Ma'n H. Zawati.

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List of Figures and Tables

List of Abbreviations

In alphabetic order

ACMG- American College of Medical Genetics and Genomics

CAGC- Canadian Association of Genetic Counsellors

CBGC- Canadian Board of Genetic Counseling

CCMG- Canadian College of Medical Geneticists

GC (GCs)- genetic counsellor/ genetic counsellors

GCAs- genetic counsellor assistants

MG (MGs)- medical geneticist/ medical geneticists

EDI- equity, diversity, and inclusion

ELSI- ethical, legal and social issues

HCP (HCPs)- health care provider/ health care providers

LMICs- low- and middle-income countries

MS/MS- Tandem Mass Spectrometry

NBS- Newborn screening

NICU (or ICU)- neonatal intensive care unit/ intensive care unit

VUS- variants of uncertain significance

WES- Whole-exome sequencing

WGS- Whole-genome sequencing

WGS-NBS- Refers to the use of whole genome sequencing in newborn screening

WHO- World Health Organization

Chapter 1: Introduction

1.1 Background

1.1.1 *History of Newborn Screening*

Screening is a preventive method that identifies individuals within a population who might be at risk of developing a health condition[1,2]. Newborn screening (NBS) is a public health program that identifies asymptomatic newborns for pre-selected conditions using a heel prick blood test[1–3]. The initial screening is followed by confirmatory diagnostic testing on individuals who were found to be at risk[4]. NBS is a World Health Organization (WHO)-approved pediatric strategy implemented across many countries[,3]. Since the creation of such programs in 1963, newborns and their families have greatly benefitted. The early detection of immediately treatable disorders has improved not only the quality of life of newborns but also, in many cases, saved their lives[5,6].

NBS programs initially screened for PKU (phenylketonuria), a genetic disorder that can lead to irreversible brain damage without immediate action[7]. The detection of PKU through NBS was incredibly successful at providing early intervention that prevented further complications for the child[8]. This achievement led to international discussions about the potential of screening newborns for other disorders at birth[8]. In 1968, The WHO published the *Wilson and Jungner Principles*[9] to justify the inclusion or exclusion of a condition in a screening program. Some of the criteria include its scientific validity (the accuracy of the test)[10], the clinical utility (is there a medical treatment, therapy or course of action for the detected disease) and the ability to access such treatment or therapy[9]. NBS programs adopted these principles and expanded their scope to include other conditions. Over time, additional disorders were incorporated into the screening program, with congenital hypothyroidism being introduced in 1974, followed by other disorders.[8].

In the 1990s, Tandem Mass Spectrometry (MS/MS), a technique used to screen for multiple disorders from one biochemical test, was introduced to NBS programs. MS/MS could detect new conditions that did not meet the *Wilson and Jungner* criteria. For example, rare disorders with no early treatment, such as *mitochondrial trifunctional protein deficiency,* could be identified with MS/MS[11]. Nevertheless, early detection had the potential to reduce the 'diagnostic odyssey' lived by patients and parents[12], a term in the literature describing the extensive period of time and the several tests families may undergo before receiving the diagnosis. In 2006, the American College of Medical Genetics and Genomics (ACMG) created a national panel to evaluate which conditions should be included in NBS programs to create a more uniform and equitable NBS program throughout different states. The discussions led to the creation of a Recommended Uniform Screening Panel (RUSP)[13], determining which conditions should be a part of NBS across the states in the US[14]. The main modification to the initial *Wilson and Jungner* criteria was that the benefit of testing was not only directly related to treatment but also to benefit the individual, the family and even society in other ways[14]. Internationally, there is still significant variability in the presence and scope of screening of public health NBS programs. For instance, the UK screens for nine conditions; in the US, the average is 35, and in Australia, 25[15]. The European Union has no consensus on the number of conditions to be included, and few countries in the Middle East and North Africa have an established NBS program[16]. The NBS program by the WHO remains one of the most successful public health programs[17,18].

In Canada, healthcare is a universal system, accessible to all and regulated by each province or territory. Thus, each respective government manages their NBS programs and has its policies, protocols, and guidelines[19]. For instance, the number of conditions screened for in a given jurisdiction could vary between 14 to 36 conditions[19]. Across all regions, NBS is voluntary,

although highly recommended, and free of cost. In Quebec, 200 newborns are identified with treatable conditions every year[1]. As new research emerges, NBS programs, guidelines, and best practices are continuously updated. Each province or territory has a panel of experts deciding the conditions in the NBS program[19].

Screening programs, such as NBS, requires the professional guidelines to provide comprehensive and well-informed direction for clinical practice. Professional bodies within Canada make recommendations or set standards that guide the implementation of policies and guidelines in each province, such as the Canadian Pediatric Society[20] or the Canadian College of Medical Geneticists (CCMG)[21]. For example, the CCMG released a statement in 2023 presenting an approach on when to perform genetic testing on children with neurodevelopmental disorders[22], which influences the practices of medical geneticists across Canada. Furthermore, international bodies also guide policies across countries, such as the WHO[3].

1.1.2 *Advancements in Genomics*

The *Human Genome Project*[23], completed in 2001, created enthusiasm for how genomics could enhance our understanding of diseases and enable the discovery of new tests and treatments for health conditions[24]. Performing genetic screening on the population for health conditions has been of high public interest since then. Outside of screening programs, the first whole exome sequencing (WES) used in the clinic to diagnose a child happened in 2009. It resulted in life-saving treatment for severe inflammatory bowel disease[25]. Researchers, clinicians, policymakers and others began questioning how genomic sequencing could improve current NBS programs: Could it fully replace traditional NBS?[26] In the USA, the *NBSeq project* attempted to implement WES in NBS to answer this research question. The results showed that WES had a 88% sensitivity and

98.4% specificity, while the sensitivity of MS/MS (the previous method) was 99% and the specificity of 99.8%[27]. WES was therefore deemed to be insufficiently sensitive to be a primary screen[27]. WES was found to be an appropriate secondary test used for diagnostic testing purposes rather than screening.

Furthermore, genetic screening could not entirely replace traditional NBS programs, as some conditions do not necessarily have a genetic cause (e.g. congenital hypothyroidism) and are well detected through metabolic tests[28]. Still today, MS/MS remains the primary method for screening for diseases in NBS. In Canada, most conditions are screened through biochemical tests. Genetic-based screening is performed only for certain conditions, varying from 1 in Quebec in Newfoundland (cystic fibrosis) to up to 9 in Ontario[19].

WES methods sequence specific regions of the genome that lead to the production of proteins in the body, which is about 1-2% of the entire genome[29,30]. Whole genome sequencing (WGS) is used to sequence the complete genome rather than targeting specific areas or variants known to cause certain diseases[29]. WES is less costly, less time-consuming, and more practical as compared to WGS. However, current research shows that WGS is better from a clinical and technical standpoint[29,30]. Today, the cost of WGS is about 1000$ (USD) per genome and is expected to continue dropping in price[31]. WES/WGS are increasingly used in the pediatric clinical context for diagnosis. For instance, they are used in neonatal intensive care units (NICU) when a child is born with congenital abnormalities, in the case of a child with undiagnosed developmental delay or for critically ill newborns[32]. Studies suggest rapid WGS in the NICU is highly effective in diagnosis and clinical management[32]. Using a new nanopore sequencing technology, the fastest time to perform WGS was five hours[33]. WGS has also shown reduced costs of care per patient if the results are made available quickly[34].

Nonetheless, genetic sequencing (including both WES/WGS) has limitations, such as its inability to detect conditions requiring methylation testing (e.g. imprinting disorders)[30]. Furthermore, the findings frequently exhibit inconclusiveness owing to variants of uncertain significance[62,75], along with inherent biases towards greater accuracy or diagnostic relevance in White populations[35]. Even when there is a diagnosis, there is a limitation on the actions/ treatments available. The molecular basis of more than 7300 genetic diseases is understood[36], while there are now about 500 known genetic diseases for which an early intervention exists and can improve patient outcomes[37,38].

With the technological development and decreased cost of WGS, discussions surrounding sequencing children at birth began to gain momentum[39]. A recent study by the *Rady Children's Institute for Genomic Medicine* found that 41% of infant deaths were related to genetic diseases in the US[40]. According to the study, a WGS diagnosis during NICU admission could have prevented mortality [40] in five out of these seven infants. Congenital malformations are among the leading causes of infant mortality in many countries[41,42]. Some believe that the broad implementation of genome sequencing in newborns could "*substantially reduce infant mortality*"[43]. In some cases, genetic screening could also prevent side effects, for example, hearing loss caused by antibiotic treatments[44]. Treatment for various genetic diseases is still limited, as drug development and treatment costs remain high. New technologies, such as gene therapy and gene editing tools (e.g. Crispr-Cas-9), are predicted to provide new treatments and therapies[45].

Genome sequencing has thus long been predicted to become part of NBS [46]. In 2015, the *BabySeq Project*[47] began to screen asymptomatic newborns using WES. This project was based on a previous genetic screening project in adults, the *MedSeq Project*[48]. The *BabySeq* study is currently ongoing and looking at the results of WES in newborns, with some results available, including psychosocial effects and the review of the clinical value of sequencing[49–52]. More recently, current pilot research studies are looking at the use of WGS. In the United States, the GUARDIAN research project (Genomic Uniform-screening Against Rare Diseases in All Newborns), launched in September 2022, aims to complete WGS in 100,000 newborns for about 160 treatable diseases[53]. Parents can opt to screen for 100 other neurodevelopmental disorders with no existing treatment. However, alternative courses of action for these conditions could benefit the child (i.e. physical therapy, occupational therapy or speech therapy) [54,55]. The conditions screened through WGS are not currently part of the standard NBS. Likewise, the United Kingdom has begun to sequence the genomes of 100,000 babies to identify treatable diseases[56], a research initiative of Genomics England in partnership with the UK's National Health Service. The conditions tested total about 200, all actionable childhood-onset conditions[57]. The variants analyzed have a clinical utility; therefore, identification would enable early treatment. The pilot studies aim to analyze the potential use of WGS and to decide whether NBS using WGS should become routine in standard clinical care in the country[58]. Similar efforts are also taking place in different hospitals in the US[59], China[60], and the European Union[61]. Standard NBS programs in the UK and US screen

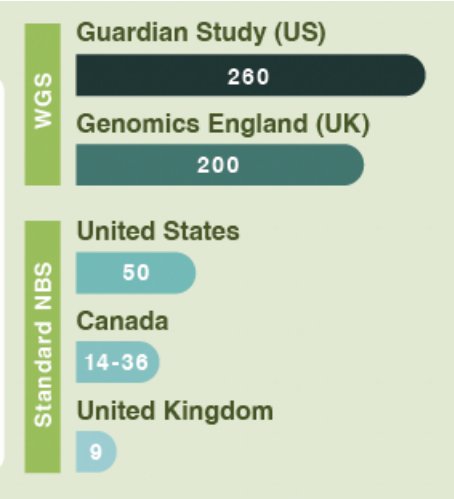

Figure 1: Number of conditions screened in Standard NBS and WGS-NBS by country.

for 9 and 50 conditions, respectively[62]. Figure 1 describes the number of conditions screened through NBS programs in standard and research pilot projects.

Clinical genetics continues to grow, with a projection of its use in clinics to have increased by 23% from 2014 to 2024[63]. The continuous decline in the cost of genetic technology and the development of new procedures are driving its increased use[31]. The pilot programs will impact the global situation of NBS programs. Indeed, recent literature has discussed that WGS is an inevitable or extremely likely next step to NBS[15,64–67]. While there may be numerous benefits to using WGS to screen newborns, it comes with many ethical issues [67,68]. In particular, WGS of newborns as a public health strategy may impact the practice of health care workers[18,64,69]. For example, the demand for genetics consults will increase, and further support for parents will be required before and after screening[70]. This section delves into the ethical considerations that revolve around NBS and genetics.

1.1.3 *The Ethics of Genetic Newborn Screening*

The best interest standard is the primary consideration in all actions concerning children, as childhood is "*entitled to special care and assistance*"[71]. In clinical practice, the best interest standard is applied when a child lacks capacity or maturity[71,72], which is evident in the case of newborns. It is widely established in pediatrics that genetic screening and testing should be offered in the child's best interest, and programs should be developed carefully, considering the possible benefits and risks[73–75]. The introduction of WGS adds new benefits and challenges to NBS[18,35]. Sequencing asymptomatic newborns is not currently performed in the standard clinical practice. It is instead used for diagnostic purposes when infants are born with congenital malformations or show symptoms of potential genetic conditions or developmental delay in the NICUs[76]. WGS-NBS programs, as a public health care strategy, will have positive and negative impacts on

children, their families, health care providers (HCPs) and the health care system[17]. Table 1 introduces some of the ethical and practical considerations regarding the use of genetics in NBS.

Table 1: Genetics in Newborn Screening- Ethical Considerations

Scope of screening	• Selecting which conditions to include and screen for (e.g. no treatment available, late-onset diseases)[8,73] • Deciding the scope of the delivery of results to patients[8,77] • The amount of information parents want may vary[78] • Managing secondary/incidental findings /variants of uncertain significance[79,80] • Managing variant interpretation without clinical evidence (asymptomatic child)[24] • Re-interpretation of variants in the future and recontacting the patient[77,81] • Managing False positives/ False negatives in the screening[77,80]
Limitation of Resources	• Ensuring fair access to the screening programs, counselling, to follow up and treatment (if available)[8] • Managing the cost of follow-up testing and treatment for affected individuals[55,82,83]. • The human right to benefit from science, including for asymptomatic babies[81] • Resource limitation- clinics already have long wait lists, including and prioritizing asymptomatic babies[24] • Research and data available for genetic conditions are mainly derived from Eurocentric populations. How can it be translated to benefit other populations?
The short and long-term impacts on	• Managing the parents' vs child's interest[80,83] • Are parents aware of the potential risks of WGS in NBS?[80,84] • Stigmatization & discrimination risks for the child[85,86] • Children identified at risk without clinical evidence may create additional uncertainty and anxiety for parents[83]. • Ensuring appropriate communication in long-term care?[83]

parents and children	• Not having access to the interpretation of specific results can lead to a prolonged diagnostic odyssey, impact family planning and unable monitoring conditions[8,12,87] • The potential psychological effects on parents and children[8,80]
Privacy and Confidentiality	• Would the data be stored? How would it be managed? For how long? [24,55,86] • Genetic discrimination[85] • Privacy of data of the child[85]

International organizations, academics and policymakers are concerned with such issues when studying the scope of NBS programs[24,68]. Integrating WGS in NBS programs may create new challenges for HCPs in direct contact with parents and their newborns[67]. For example, it could create additional issues in managing, interpreting, and communicating to patients the large amounts of data generated by the screening test[81]. Gaining a deeper understanding of the impact of WGS-NBS in the practice of HCPs is imperative for its proper implementation in the future[67]. The upcoming section will delve into the role of genetic counsellors, a crucial stakeholder in the provision of genetic services in clinics, particularly in pre and post- test counselling.

1.1.4 *The Practice of Genetic Counsellors*

Genetic counsellors (GCs) are health care providers with specialized training in genetic conditions and counselling[88]. Their responsibilities generally include guiding patients through the screening and diagnosis process, analyzing and interpreting the results of genetic tests and identifying individuals at risk for genetic conditions[70,89]. They offer psychosocial counselling and help patients and families understand the medical and personal implications of genetic diseases[90]. Genetic counselling is strongly recommended for pre and post-test of genetic disorders[91,92].

Through non-directive counselling, patients can be informed about the types of genetic tests, the appropriate time to do the test and the potential findings. Patients can decide whether to proceed with testing and the options/treatments available after testing[93].

The role of GCs may vary by institution and position[70], and some of their skills may be seen as complementary to that of the medical geneticist[94]. Medical geneticists are physicians involved in diagnosing, managing and caring for patients with genetic disorders[95]. GCs' responsibilities primarily focus on communicating with patients and providing counselling compared to medical geneticists[94]. There is an increased demand for the services provided by genetic counsellors globally[93,96]. This demand for their services will continue expanding with the inclusion of genome sequencing in the clinics[97]. New genetic counselling models have already been adopted to meet the needs of clinical genetics, such as group genetic counselling, co-counselling by GC and MGs and telehealth services[70]. However, waitlists to see one remain long[70].

In Canada, genetic testing in children (including newborns) should be accompanied by appropriate genetic counselling according to the Canadian Pediatric Society[92]. In the NBS context, GCs provide counseling to parents following a positive or abnormal screening result for a genetic condition[98]. For example, in Ontario, GCs are actively involved and part of the clinical team of the Newborn Screening Ontario Program[99]. GCs may also be part of a screening laboratory[100]. Their presence in NBS programs is expected to increase with the use of genetic technology[15,64,69]. As all newborns will undergo genetic screening, GCs will face increased demand for consults[65,70,101,102]. This will create challenges for their practice, such as defining their roles and responsibilities[81]. Indeed, WGS will challenge the counselling, prognosis, and follow-up in the clinics[70,81]. For example, GCs have expressed apprehensions regarding the structure of the counseling process in the context of WGS[103]. These concerns stem from factors such as the

substantial volume of generated data, the presence of VUS leading to result uncertainty, limited treatment and interventions available , and the ethical and psychological dimensions embedded within counseling sessions[103].

The formulation of new guidelines and standards of practice for GCs will be necessary in the context of WGS-NBS[26]. For instance, there are no guidelines on the best clinical practice for asymptomatic children whose WGS indicates a potential genetic disease[104]. They may also struggle with managing and delivering results, as WGS creates significant amounts of information, for which many are classified as variants of unknown significance (VUS)[64,76,102,105]. The current ethical and counselling guidelines used for NBS programs may not reflect the inclusion of WGS into NBS programs and requires further investigation[85].

In Canada, WGS/WES are currently used as diagnostic tools for newborns who are critically ill at the NICUs [106]. Could genetic screening of newborns using WGS be implemented for all newborns in Canada in the future? The predicted cost-efficiency of WGS, the rise of research projects internationally on WGS-NBS, and global discussions surrounding its potential suggest a strong probability[34]. Furthermore, there is interest in adding genetic conditions to screening panels in the country[19]. For example, spinal muscular atrophy has been recently included across five provinces[19]. It may be a matter of time before Canadian NBS programs consider using WGS. From a clinical standpoint, it is imperative to address the feasibility and ethical issues raised by this. GCs, in particular, are key stakeholders in the delivery of genetic services. They would be particularly involved in the pre and post-counselling of families following a WGS-NBS[15,64,69]. Would Canadian GCs be ready for such changes in the standard clinical care?

1.2 Research Question and Objectives

Screening, diagnosing, managing and treating procedures are continuously refined through research and progress in genetics[107]. At present, WGS-NBS is being studied in the research setting, with the objective of possible expansion to the clinics in the future in certain countries. However, as discussed in the section above, various ethical issues are raised with its use.

GCs are expected to play a crucial role in the future in providing counselling to parents after NBS results[15,64,69]. Recent research in Canada demonstrates the need to integrate further GCs into the neonatal care team to counsel parents[108]. The vulnerable position of families upon the birth of a child, as well as the restricted time frame for contact, the need to whether to allow WGS screening for their child and decision-making upon the announcement of sequencing results (which require confirmation and diagnosis) and possible treatments must be taken into consideration by GCs. There is an evident need for policies to guide the introduction of WGS into population-based NBS programs[109]. As GCs will play a key role in counselling families in WGS-NBS[15,64,69], this research project aims to answer the following question:

How will the duties of genetic counsellors in Canada be challenged by the implementation of whole genome sequencing in newborn screening programs?

This research intends to understand the ensuing ethical concerns in WGS-NBS and how they fare with the practice of GCs. The future of newborns and their families may be impacted by the genetic information revealed at birth[103]. Thus, the potential benefits and harms for newborns and their families form this research's driving force. NBS is one of the least discussed topics in the genetic counselling literature, only examined in 1.9% of articles in the *Journal of Genetic Counselling*[110]. This gap emphasizes the need for research and discussion on the topic. There is a need for a Canadian perspective on the ethical issues that GCs may face in NBS programs in the advent of WGS. Are Canadian GCs well prepared for the potential risks and challenges of WGS

in NBS? This thesis explores if the traditional ethical duties of GCs still hold with the advent of this new technology.

The overarching goal of this research project is to contribute to the field of genetic counselling by elucidating ethical considerations and how they can impact daily clinical practice, where GCs might face different ethical dilemmas. This thesis aims to:

1. To examine the literature available on ethical considerations posed by whole genome sequencing (WGS) in newborn screening (NBS) and how they might impact the practice of genetic counsellors (GCs).
2. To understand how WGS-NBS fares with the current ethical duties of Canadian GCs and identify new policy concerns that may arise.
3. To reflect on how GCs in Canada could approach WGS-NBS based on the current duties, guidelines, and Code of Ethics and how they might be updated to reflect the identified ethical and policy challenges.

This study will interest GCs, scholars in bioethics, policymakers, provincial screening laboratories and other HCPs involved in the provision of NBS, such as medical geneticists. This research relates to bioethics, a multidisciplinary field that supports the study of ethical, legal and social issues (ELSI) through research to develop knowledge that can produce a meaningful impact in policy and clinical practice. This thesis does not discuss whether WGS in NBS should become a public health strategy in Canada. It limits itself to examining the practice of GCs and does not review the duties of physicians or other health professionals, which are beyond its scope. The role of the GC is explored within the healthcare context and not in the research or industry settings.

Chapter 2: Methodology

2.1 Methodology Overview

First, a literature search contextualizes the topic, starting by situating NBS in a historical setting, researching the use of genetics in the newborn context, exploring the ethical issues that ensued and introducing the role of GCs. The results are presented in Chapter 1, in the background section. The results of a narrative literature review on ethical issues posed by WGS-NBS and their impact in clinical practice are presented through a thematic analysis in Chapter 3. Ethical normative documents (guidelines and policies) for GCs in Canada are examined to describe their duties from an ethical perspective in Chapter 4.

Finally, the results from Chapters 3 and 4 serve as a foundation for creating points to consider developed in Chapter 5. More specifically, the later chapter proposes points to consider for Canadian GCs in the context of WGS-NBS based on ethical and practical concerns. Finally, Chapter 6 summarizes the findings throughout this thesis and proposes future directions for research in this area.

2.2 Research Design

2.2.1 Narrative Literature Review

The purpose of a narrative literature review is to summarize published literature on a topic and to illustrate the current state of the literature[111]. A narrative review may also be used to identify possible future research topics[111]. They may be a valuable approach for assessing literature within a historical context, which is the case for NBS. This narrative review aimed to explore the ethical considerations in clinical practice faced by GCs in the NBS context with the implementation of

genetic sequencing. It also aimed at understanding how GCs will address the needs of patients and their families receiving such care. A PRISMA flow chart reports the process of screening and selection of articles (Figure 2).

The literature was identified by searching the PubMed and Scopus databases. The primary search terms used were (((genetic counsel*) AND (newborn screening)) AND (sequenc*)) AND (ethic*). Sequenc* rather than "whole genome sequencing" was chosen to expand the number of results and observe how other types of genetic sequencing have been approached so far in the clinics. No filter was applied for the dates to understand the historical context of NBS and the ethical issues raised in the literature in the past. Ethic* was chosen as a keyword; otherwise, the search results yielded various scientific articles that do not relate to the research question and discuss ethical issues. Genetic counsel* was chosen as a keyword to identify the articles discussing genetic counselling in the NBS context. The identified articles also discussed the role and ethical issues faced by other HCPs involved in NBS, such as medical geneticists. These articles were included in the review to gain a more comprehensive understanding of the ethical considerations in clinical practice, considering the limited role of GCs within NBS. The initial search was concluded on March 28th, 2023. The search was open to articles from international sources, as the literature on the topic is already narrow.

The search results were assessed for eligibility by screening titles and abstracts and then screening full-text articles. Publications were initially included if they discussed genetic counselling in the context of newborns and genetic sequencing. The articles included also must have discussed ELSI. When screening the full-text articles, publications were excluded if they did not sufficiently discuss the ethical challenges in clinical practice in newborn genetic screening.

Verifying the references of identified articles to include them in the review exercise was valuable. This citation-chaining process[112] identified additional sources, although a saturation point was reached when no new sources were identified[113].

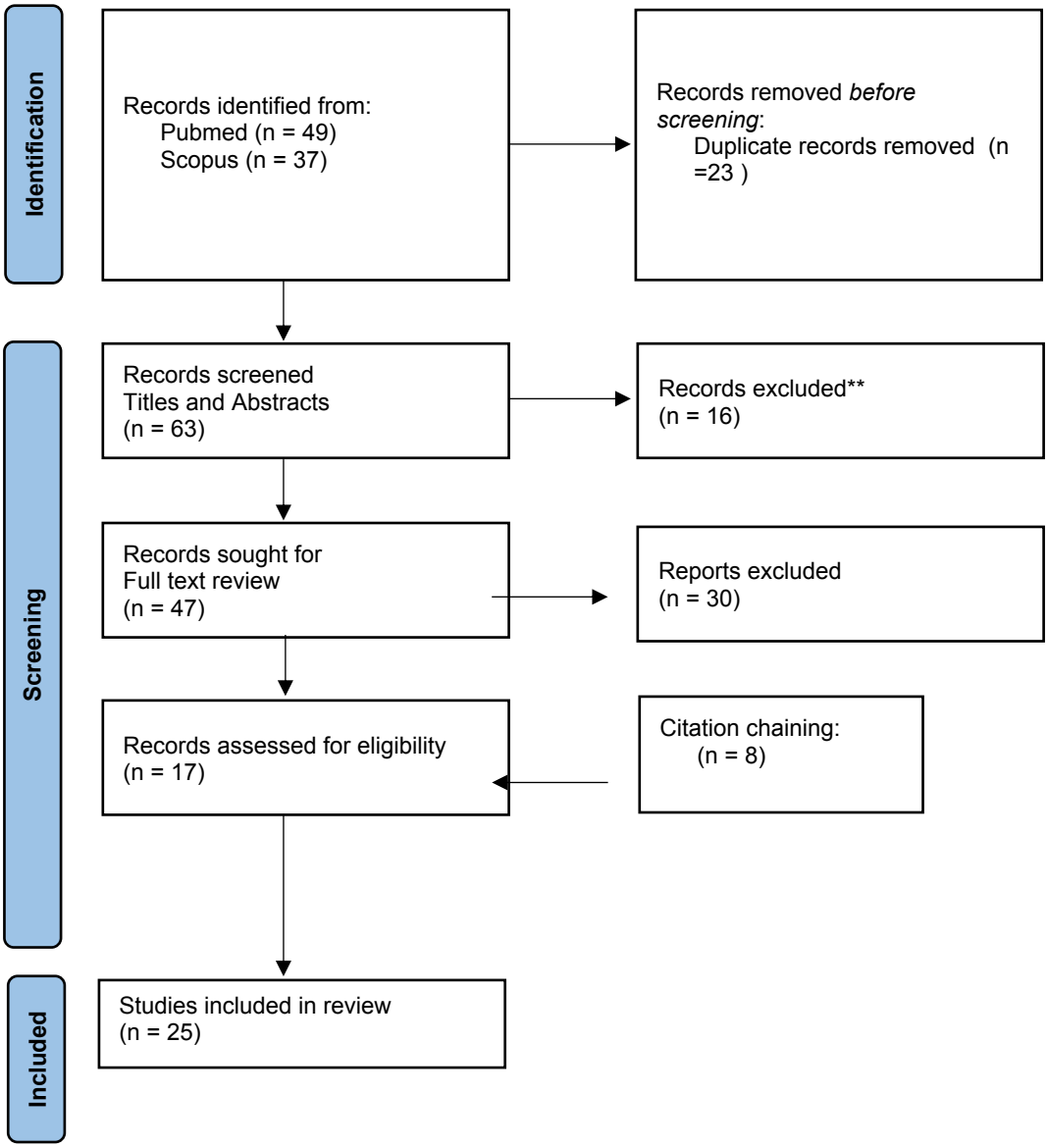

Figure 2: PRISMA FLOW CHART- narrative literature review

2.2.2 Thematic Analysis

The results of a narrative review may be presented as a '*conceptual frame,'* where the content is separated into different concepts/variables[111]. A thematic analysis was performed to identify the central ethical issues discussed in the literature, a common approach to identify patterns within a dataset, such as a body of literature[114]. Thematic analysis is a foundational method for qualitative analysis. It can contribute to a deeper understanding of the topic, generate unexpected insights and help produce an analysis that informs policy[115]. These all relate to my objectives to examine and understand the literature surrounding ethical considerations and to create points to consider for policy. Furthermore, thematic analysis is a standard method used in genetic counselling research[114].

The Braun and Clarke guidelines for reflexive thematic analysis[115] were followed to identify the essential themes across the literature. First, the author became familiar with the literature during the initial screening and notetaking. Potential codes for primary and secondary themes of articles were noted in a spreadsheet. Initial codes were then generated (e.g. difficulties in interpretation of VUS, stress lived by families post-results, limited staff issues). These codes were sorted into themes, then tested to ensure they were sufficiently discussed in the selected articles. Some themes were clustered into one primary theme as they related to each other (e.g. interpreting, managing and communicating results have similar issues). The thematic content analysis resulted in five primary ethical considerations for implementing WGS in NBS in clinical practice. The articles included were from three main categories: the view of HCPs who deliver genetic counselling on WGS and NBS, the view of parents who have had WGS for their newborn and finally, articles broadly discussing ELSI for HCPs on WGS. Chapter 3 summarizes the main findings of the thematic analysis.

2.2.3 Identification of Ethical Normative Documents on the Duties of Genetic Counsellors

The role of GCs, in the context of this thesis, is not described from a practical standpoint but rather from an ethical stance. Consequently, the role is characterized by their ethical duties. The duties of GCs in Canada can be identified through different normative documents. Normative documents provide guidance to specific stakeholders and usually set standards and practices. Regulations can also be included in this definition (as legal norms)[116]. This research, however, focused on the identification of ethical normative documents. The documents were identified from the website of their professional organizations, the Canadian Board of Genetic Counseling (CBGC) and Canadian Association of Genetic Counsellors (CAGC), completed on April 17th, 2023. The ethical duties of GCs in Canada are mainly described in the following documents Code of Ethics for Canadian Genetic Counsellors (2006)[117], CAGC Practice-Based Competencies[88] and CAGC Knowledge-Based Competencies[118].

The Code of Ethics describes their duties toward patients, their colleagues, themselves, and society. The Knowledge-Based Competencies and Practice-Based Competencies form the baseline for developing practice guidelines, curricula for GC students and certification standards[119]. The Practice and Knowledge-Based Competencies together form the basis for developing further practice standards. They were both written with the expectation that GCs would become regulated in Canada. The Practice Based Competencies document has been analyzed for validity[119].

2.2.4 Identification of Literature on the Role of Canadian Genetic Counsellors

Additional literature on the role and duties of genetic counsellors in Canada was identified through Scopus and PubMed, a Basic Google Search, and the Canadian Medical Association (CMA)' PolicyBase finder. Search words included "Genetic counsel*" AND "Canada" OR

"Canadian* AND "Policy" AND "Role" AND "Ethics." Research related to the US was excluded as the main interest of this thesis was Canadian GCs. Citation chaining enabled the discovery of additional literature. This is not an extensive list of all the literature on genetic counselling in Canada. It instead helped the understanding of the role of GCs in Canada, which is presented in Chapter 4. Literature in both English and French was included.

2.3 Limitations of Research

The limitations of the chosen methodology and the analysis are described in this section. First, the narrative review enables the discovery and analysis of some of the ethical issues faced by GCs and other HCPs in the WGS-NBS context. However, a narrative review may not include an exhaustive list of all potential ethical concerns WGS-NBS poses. The initial systematic search (i.e. the PRISMA Flow Chart) with specific keywords could have overlooked some publications. It could have led to overinflating specific themes and understating others. Furthermore, this thesis did not review legal publications, legislation, or court decisions on the topic.

Due to the extent of ethical issues covered in this thesis, it was not possible to explore each in depth. The points to consider in Chapter 5 were created within the constraints of the narrative review, the thematic analysis and the ethical documents identified. Therefore, they may be limited and require further research, stakeholder engagement and validation.

Author's Reflexivity

As a graduate student in bioethics, the author approaches the topic with an ethical perspective, seeking to explore the ethical implications of newborn screening from an academic and research standpoint. The author does not have experience in genetic counselling and its practicality. She

attempted to address by asking for informal insight as well as feedback from genetic counsellors in two different provinces to better understand and contextualize current practices.

WGS in NBS causes controversy among clinicians, researchers, bioethicists, and various stakeholders. Articles frequently present divergent standpoints regarding the support for WGS-NBS. The PRISMA flow chart procedure aimed to reduce the selection bias and confirmation bias in narrative literature reviews. Furthermore, the thematic analysis can be influenced by personal biases, which may cause themes to be overemphasized or understated. In an effort to mitigate biases in the discussion, the author of this thesis actively participated in conferences and talks related to the topic. She made an earnest attempt to address both the positive and concerning aspects of WGS-NBS in their research.

Chapter 3: Results- Ethical Implications for Genetic Counsellors in a WGS-NBS Context

The following section presents the results of the narrative literature review, which aimed to understand and summarize the ethical implications of WGS-NBS in the clinical context. Through a thematic analysis, the following themes were identified: (1) interpreting, managing, and communicating results; (2) psychosocial and long-term risks; (3) challenges in informed consent; (4) practical challenges and (5) EDI and accessibility. It is not meant to be an exhaustive list of issues that GCs may face in the advent of WGS-NBS, but one reflected in the body of literature. The five themes will be described in depth drawing upon the knowledge from the narrative literature review. Table 2 describes the final themes and subthemes used to create a report that illustrates these themes.

Table 2: Themes and Subthemes Identified in the Body of Literature.

Themes	**Long-term psychosocial risks**	**Interpreting, managing, and communicating results**	**Informed Consent**	**Practical challenges**	**EDI & Accessibility**
Codes	○ genetic discrimination ○ stigmatization of child because of disability ○ stress/anxiety to parents ○ stress to child ○ medicalization of child ○ need for long-term counselling	○ large amounts of data ○ VUS ○ positive/ negative/ unconclusive results ○ delivering results in a concise manner ○ communication	○ pre-counselling ○ consent of child ○ understanding of genetics ○ stress/anxiety/ emotional load ○ vulnerability ○ genetic literacy	○ other HCPs not trained in genetics ○ overburden the system/ripple effect on the system ○ Professional regulation ○ Lack of guidelines	○ Costs ○ Disparities between jurisdictions ○ Accessibility of treatment ○ Marginalized populations

3.1 Interpreting, Managing and Communicating Results.

While WGS enables screening of several genetic conditions, it will also generate a large quantity of data to be interpreted, managed and communicated[76,101,120]. WGS provides information on the entire genome sequence, yet the limited knowledge of many properties of the human genome may directly impact clinical practice. For example, several variants and structural variants within the genome are poorly understood (i.e. VUS) [64]. Interpreting WGS results with several VUSs will be a clinical challenge for GCs and other HCPs[64,76,102,105]. Only specific VUS are returned to parents in Canada based on CCMG guidelines[121]. According to a study, 35% of healthcare professionals (HCPs) reported difficulty interpreting ambiguous findings[122]. MGs in Bulgaria emphasized their concern with WGS generating lots of unclear information[123]. There are databases such as ClinVar[124] or LOVD[125] to assist in analyzing gene variants, which include mainly exome variants but exclude intronic ones (which can be detected through WGS). Intronic variants may complicate the ability to provide post-WGS counselling to families[126]. Explaining VUS of WES has already been demonstrated to be complex by clinicians in the hearing loss context:

"One thing we've found is that there seems to be … lots of variants (of uncertain significance) in hearing loss genes. So, it's quite common to get a report with three or four variants of unknown significance. Or even one that we're quite confident is the diagnosis and some variants of unknown significance. And I found that very challenging for some families, to explain a genetic finding and then explain other genetic findings that may be less relevant.[127]*"*

Results from WGS may be inconclusive, ambiguous and complex, impacting HCPs' ability to interpret them[120]. For instance, even in the case of known variants, there is a spectrum of phenotypes due to the penetrance of the genotype[102,105,109]. The same variant can present different symptoms and require other treatments and interventions[120]. This is the case in some hearing loss

disorders[127], where cochlear implantation may not be effective for all, and learning sign language might have been preferable management of the condition depending on the phenotype[28]. Furthermore, Pompe's disease is controversial because it is not included in standard NBS programs. The phenotype of Pompe's disease has a variable onset (infantile vs late) and phenotypic variability[69]. Although the genotype-phenotype relationship is unclear, the clinical management is well established[69]. Knowing in advance about the disorder is crucial to enable quick treatment once the symptoms develop.

Other interpretation challenges include the dynamic landscape of genetics, with ongoing new genetic discoveries requiring re-interpreting results[76,126]. From a clinical perspective, that also requires constant learning from the part of GCs and other HCPs. However, their ability to remain current with extensive, continuously changing information is limited. Some suggest that the ability to manage and interpret results at the moment might not be sufficient for the WGS-NBS implementation[35].

There is much debate within the genetic community about managing results and what information should be shared with parents. Although the best interest of the child standard is applied in NBS, it has received criticism in the past for being applied inconsistently, being vague and providing little guidance to HCPs[102,128]. In the WGS-NBS context, clear guidelines on the return of results to parents would be required[101]. HCPs in one of the studies emphasized the importance of maintaining the exact scope of screening as traditional NBS:

"You have to apply the same criteria we apply currently to newborn screening…the disease has to be treatable and has to have a pre-symptomatic phase, and that early intervention results in improved outcome"[15].

There is an obligation to return clinically important information that is actionable during childhood. However, disorders such as late-onset disorders (e.g. neurodegenerative) that could be screened through WGS are not included in NBS[122], as they are not considered in the child's best interest to communicate such results to families[76]. Several policy statements, including from the American Society of Human Genetics (ASHG), have discouraged the return of late-onset disorders[129]. However, not disclosing results fails to warn the parents and other family members who could have pursued preventive measures[18]. Secondary results or incidental findings, such as carrier status, are highly debatable topics in the literature[65,67,76,105]. For instance, BRCA1 mutations (i.e. a variant that increases the risk of breast cancer) are not disclosed as it is considered a late-onset disorder and not actionable to the child but could be actionable for the mother. The ethical dilemma involves protecting the child's right to an open future or the potential to warn other family members of actionable conditions[69,76].

Furthermore, the genetic literacy of patients can limit the ability of GCs to communicate results[101]. Genetic information is of high complexity, and the newborn period is already a stressful and busy time for new parents[130]. Their ability to manage complexity and uncertainty may vary[130]. Parents may be less comfortable with the unknown and want to learn as much as possible about their child's health. Additionally, knowing or not knowing the risk your child may carry for a particular disease can be stressful for some families[18]. Parents may have varying preferences regarding the amount of information they want to receive.[120] Moreover, knowing a diagnosis early has a "personal utility" for patients and their families beyond the test results[24]. This has been seen as a justification to include conditions in NBS programs. A move from clinical utility to personal utility could expand the number of results provided to patients with NBS in the future[18].

In a study in China, 81% of HCPs showed interest in using sequencing technologies in NBS, yet 73% of participants were worried about their ability to provide counselling in this context, particularly due to the large amount of genetic information created, lack of treatment or interventions available, the accuracy of the technology (including cost and reporting time) and the psychological burden it might cause [103]. There is a need to develop communication and counselling strategies for GCs and other HCPs involved in treating patients regarding WGS[102,105,130]. According to the literature, the communication of screening results should be well-defined in an NBS context where parents are already highly vulnerable[120]. GCs will likely be significantly involved in communicating and interpreting the results of WGS-NBS[64,76]. The large amount of data produced from WGS would be challenging to communicate in a sensitive and stressful period for parents[126]. The extensive counselling required post-WGS was not seen as a cost-effective process[64,123]. There are moral/professional obligations to disclose certain information to parents, and policy is needed to guide HCPs through announcing NBS program results[101]. Interpersonal communication, a strategy used by GCs, could be an approach to adapt to the need of each patient. However, this communication strategy is time-consuming and may not apply in a WGS-NBS context where all newborns would be screened and many would require counselling sessions[130].

To overcome communication barriers, one practical approach is to provide patients with information in simple language that is easy to understand. This can help improve their literacy and comprehension. Lewis et al. (2018) propose that investing in long-term educational campaigns at both national and community levels could be an effective strategy to enhance the overall public understanding of genomics within a population[130]. Basic communication skills such as delivering the most critical information first, using lists, summarization and explaining technical terms should

be used. The communication-science principle describes adapting to people's needs by understanding where (i.e. sources) and how they look for information and communicate.

Two articles[109] suggested a collaborative model between patients or "peer support" for parents-to-be or new parents. Parents are likely to want to discuss NBS outside of the clinical setting. Translating basic science into tools, knowledge and resources for patients is essential to enable HCPs to assist families through WGS-NBS[130]. The success of NBS programs should be measured by the number of diseases identified and the ability to provide appropriate communication[66,105]. Other strategies include group counselling and decision aids[76]. GCs can be involved in developing documents and guidelines that will facilitate communication[105]*: "These include evidence-based standards for informed consent, improved educational materials for patients and families and new communication paradigms for genetic counsellors and other healthcare providers."*[122]

3.2 Psychosocial and Long-term Risks

The literature emphasized that sharing information from WGS with newborns and their families could cause psychological harm.[76,129] Psychological distress was a concern for most patients (78%) in a study looking at the parents' perception concerning WGS[126] . First, the uncertainty of results can be a source of stress for new parents. There is also the risk of false positive results, which may create anxiety[66,76,129]. In previous research, mothers who received false positives were likelier to report a parent-child dysfunction than controls[109]. Uncertainty, anxiety and stress may have a long-term impact on the relationship the parents develop with their child: the early "medicalization" of the child may lead to a perceived "child vulnerability," where the parent consistently sees their child as medically vulnerable following a medical situation[129].

This perception of child vulnerability has been reported to negatively impact the child's development (e.g. delays in development, anxiety symptoms and behavioural problems)[129]. Parents may also feel overwhelmed by the medicalization process:

"Yeah, well, that's the thing. Like, I don't feel like—now, in our first year it was a lot of new information thrown at us all the time. He had 86 doctor's appointments in 10 months."[109]

Furthermore, receiving positive results can lead parents to self-blame. Since genetics is familial, parents may feel guilt for passing undesired traits to their children or may even blame their partners[129]. This has been shown to affect the bonding relationship between parents and their newborns[129].

Parents may not receive appropriate psychosocial support due to resource limitations[109]. While WGS in NBS offers many benefits, it can also strain the healthcare system due to the increased number of patients and resources needed.[66] In 2017, a study on healthy adults used WGS to identify genetic modifications in their genome that could potentially result in disorder phenotypes. However, these adults were asymptomatic and healthy, questioning the clinical value of WGS in a healthy population[131]. The concern also applies to newborn screening, as it can be confusing and stressful for parents when their baby's screening results show positive, but they do not exhibit any phenotype. It is a particular worry for public health that asymptomatic patients may require clinical resources, mainly since these resources are already limited. Asymptomatic children whose screening results returned positive may be put on a waiting list or be less prioritized[28].

It is suggested that the healthcare system should not only identify those at risk but also provide them with access to appropriate resources[28]. The early results of the BabySeq project, which used WES as a screening method in both asymptomatic and children in the ICU, found "*no evidence of persistent negative effect of nGS on families"* after ten months of result disclosure on over 500

parents[51]. To achieve this conclusion, they measured mother and infant bonding, psychological distress of parents and parents' relationship[51]. The authors acknowledge that parents who agreed to participate in this study already had a more positive attitude towards research, therefore creating a sampling bias that might not be reflective of a state NBS program that would include NBS. The longitudinal impacts of WGS in newborns have not been studied yet, especially the effects on the children themselves[129].

From a different perspective, the early diagnosis following the screening of a disorder could reduce the *diagnostic odyssey* lived by parents, a long and stressful psychological experience[28,69]. A study in Canada reported parents' positive attitude towards WGS in the NICU context, where having results led them to experience relief and help prepare for the future[106]. They felt low *decisional regret* towards their decision to perform WGS. The ability to "know what to expect" felt recomforting and provided context to parents living difficult experiences. Parents simultaneously expressed frustration and surprise when diagnosed with rare genetic diseases, which may imply they were not fully aware of the potential risks of WGS[106]. Furthermore, research has shown that Canadian parents have different incentives and concerns for choosing to do newborn WGS/WES, which suggests that how they cope with results differ[106]. However, these were the results in a NICU context, where infants already have medical concerns, as opposed to asymptomatic testing in a population screening program.

Parents who have undergone thorough sequencing for their newborns often feel lost regarding the future and have requested continuous and long-term counselling and other resources[102,109,132]. The *diagnostic odyssey* does not end where the results of tests are received, but some have considered the "*diagnostic odyssey continuum*"[109]. Should long-term care be available, GCs will play an essential role in the long-term follow-up of the children[67]. Genetic counselling is an integral

component of managing these psychological effects[76,105]. GCs and other HCPs must consider how to mitigate this psychological stress that parents may face when receiving NBS results[76]. HCPs also face issues handling uncertainty in practice, which may impact clinical management[120]. They may tend to be cautious and avoid taking risks, leading to preferring overtreatment rather than missing a potential health condition, especially in a newborn screening practice[120]. Establishing clear guidelines and policies is necessary to properly assist GCs and other HCPs in addressing their patients' long-term medical, education, and social needs in the WGS-NBS context.[35,67]

In the long-term, another psychosocial risk for newborns is the possibility of facing stigmatization, discrimination, and genetic discrimination in the future. Stigmatization is "*identifying and marking an undesirable characteristic in a way that narrows a person's social identity to that characteristic*"[133]. Discrimination is *"an action or a decision that treats a person or a group badly for a reason such as their race, age or disability."* People can be stigmatized or discriminated against because of their physical condition, mental health condition, gender, race, religion, etc. Genetic discrimination refers to the *"unequal treatment of individuals based on an aspect of their genetic code or genome, such as the risk for genetic disorder*."[134]

The disability community and advocates for disability rights have raised their concern that genetic technologies may emphasize and further propagate stigmatization of and discrimination against disabled people in the social and medical contexts[126] . Past unethical practices within the medical field have led to the mistreatment and harm of individuals with disabilities and mental health disorders[135]. Some of these medical practices were considered eugenics. Similar concerns have been raised by clinicians, academics and patients surrounding the implementation of WGS in NBS [85,123]. Including certain conditions in NBS programs may reinforce discrimination. For

example, if hearing loss was included in screening methods, it could strengthen the perception of deafness as a disability[127].

If WGS is used in NBS, newborns may be at risk of being stigmatized and defined by their conditions from a very young age. They may face a higher likelihood of experiencing genetic discrimination if appropriate policies and laws are not implemented to prevent that insurance companies or employers do not discriminate against them based on genetic information [66,101,122,126]. There are concerns that whole genome screening in NBS could lead to the *"next generation of eugenics*"[85] and that it might conflict with the duty to protect patients by physicians. The literature discusses the potential aggravation of the situation:

"There is a growing need, then, for clinicians and bioethicists to consider how the clinical use of WGS in the newborn period might exacerbate these potential harms to persons with disabilities."[126]

One of the studies in the review discussed the role GCs and other HCPs might have in reducing the potential stigmatization and discrimination toward disability[126]. It raised the potential implicit negative bias that HCPs might have regarding disability and that it may impact the counselling provided to families[126]. This may be more present in the case of novel genetic variants where little information is available. A suggestion by the author was to ensure that counselling is provided by taking into account the experiences and views of the community of patients and families with disabilities [126]. Collaboration between patients' communities and HCPs is a crucial step forward. A different counselling approach might help reduce the potential bias that parents might have themselves and better inform them of what living with a disability/ having a child with a disability is like. The following quote describes the potential role GCs and other HCPs could have in reducing stigma and discrimination:

"By actively soliciting and compassionately listening to the real experiences and perspectives of disabled persons and their families, clinicians and bioethicists might rebuild trust between the medical and disability communities. Awareness of and sensitivity to the experiences of persons living with disabilities may help clinicians provide better individualized care and more effective counselling to families of acutely ill newborns who receive WGS"[126].

They must also be aware of the variability of the quality of life of people with a disability:

"assumptions about the quality of life of persons with profound disabilities may be responsible, at least in part, for families' and clinicians' decisions to discontinue life-sustaining interventions.[126]

Collaborations with the disability community can also be beneficial in situations of variants of uncertain significance (VUS) where the clinicians and GCs themselves may be unsure of the phenotype of the child, but that patient communities can be knowledgeable on the spectrum of disability, as well as the variety of resources available for their child. Furthermore, HCPs could advocate in the medical community for removing obstacles and increasing access to care and resources for newborns and persons with disability[126]. Reducing the discrimination and stigmatization within the hospital and medical care may have a broader impact on the perspectives of society.

3.3 Informed Consent

Informed consent is a central concept of medical ethics. It is defined as the patient's ability to make decisions based on a sufficient understanding of information[136]. Genetic technologies and developments in the past have challenged informed consent[123]. In the context of NBS, the parents are responsible for the consent on behalf of their infant. Newborns cannot provide consent, which may lead to the possibility that, in the future, they will disagree with the choices made for them[129]. Therefore, preparing parents to make informed decisions is imperative, especially in the newborn and pediatric context[76,130]. Genetic counselling is instrumental in conveying information to

patients pre-screening to reach informed consent[109]. However, concerns about parents' ability to provide informed consent in such a vulnerable time have been raised. For example, parents may suffer acute stress when receiving news of their NBS results, impacting their processing and decision-making abilities.[84]

One of the articles suggested that parents' decision-making is influenced by "inflicted ought"[122], a feeling of a moral obligation to learn as much as possible about the complete set of risks for their children, no matter how this might impact them. Their informed consent is influenced by the responsibility they may feel as parents, which affects their attitudes regarding obtaining results from WGS[122]. The newborn period is time sensitive, which may pressure parents into making hurried decisions. Parents are often called upon to make difficult decisions regarding screening, testing, and treatments.[109] Counselling in this context will require informing parents of the potential medical management of results[76]. For example, specific therapies may be risky and require invasive interventions but may ultimately improve their child's quality of life. Decision-aids or decision-support tools are evidence-based methods that could be useful in the decision-making process for parents, and one article suggests that they could be implemented during pregnancy to prepare parents ahead of NBS[130].

Furthermore, the familial nature of genetics impact how informed consent is obtained in the newborn context. The test results may have implications for parents, specifically relevant secondary variants, siblings and even more distant relatives[102,122]. The two values in conflict are respecting the child's confidentiality and right to an open future, with the HCP's responsibility to disclose actionable disease risk information to the family[69].

According to parents, being informed is fundamental to ensure the best care for their child, especially when it is a long-term disorder: "Become *informed, because you're going to have to be*

an advocate when your child has a rare disease."[109] Parents will continue to educate themselves about their child's condition or specific variant, even if the diagnosis is uncertain or inconclusive. Parents and caregivers of newborns have expressed their need for additional educational resources for themselves and other HCPs who are not trained in genetics but may care for children with genetic conditions (e.g. pediatricians)[105]. They also request empowerment programs and more access to multidisciplinary specialists, such as GCs[109]. Additional educational and extensive counselling will be required to obtain informed consent[64,67,105].

Parents described in previous interviews that learning and understanding their child's conditions is a long-term process[132,137]. A study found that GCs would be essential in developing educational material to facilitate obtaining informed consent and returning results to patients following WGS-NBS[15]. Over, genetic literacy plays a role in influencing the ability to provide informed consent[101]. The results of WGS are of high complexity, which may impact the family's decision-making ability. They require additional support in this process through counselling.

Before the discussions surrounding the use of genetics in NBS, the need to include consent before NBS had already been questioned[18]. Studies have revealed that few parents recall performing traditional NBS on their children, and even fewer comprehended its purpose[66]. As a result, many questioned the necessity of obtaining consent[66]. No Bulgarian geneticists supported the idea of WGS becoming mandatory in NBS in the study by Iskrov et al[123]. Their main concern was focused on the impact of genetic information on the newborn and their right not to be informed about it[123]. HCPs, overall, agreed that WGS-NBS should not be mandatory[65]. In the US, there has been more demand for knowledge and choice concerning NBS by the public[18]. In both Australian studies, most HCPs agreed it should be an opt-in program[15,67]. A suggested approach for WGS has been to obtain consent only when the clinical utility of a result is less certain[18,69].

The consent process would need to accommodate WGS-NBS, including a pre-counselling process [65,123]. The potential customizability of screening programs to parents' choices has also been considered to enhance the autonomy of parents[120,123]. Parents may have different needs to make informed choices[109,122]. A common question in this context is how much deference should be given to parents when choosing which screenings to perform and which conditions to screen for[18]. For example, parents may want to opt-in to know about specific conditions, even if no treatment is available. 83% of parents in one of the studies valued WGS because they "wanted answers" for their child's condition[115]. About half of them perceived WGS as a way that might help with access to better treatments and enable family planning[28,101]. Some parents also valued contributing to the advancement of science[122]. To implement WGS-NBS, there will need to be a balance between the personal choice of parents and clear professional guidelines to deliver results[138]. Guidance to help patients and their families make informed decisions is a critical component of WGS-NBS.

3.4 Practical Challenges

The literature highlighted that HCPs generally feel they need to prepare to support parents through the additional complexities that WGS in NBS will create[64,123]. GCs, in particular, demanded additional training concerning WES/WGS in the context of NBS[64,123]. They have requested clear guidelines for the counselling process:

"To feel "prepared" to counsel in these situations, I'd really need a solid clinical plan, preferably agreed-upon in advance by the clinical team, about what we'll do in these specific instances. What will we tell families? How long will we continue to follow these infants (in the absence of symptoms)? Depending on the condition, potentially contacting laboratories and having a plan in place for confirmatory assays to test these variants."[64]

The limited amount of GCs available to provide counselling and support was identified as a practical barrier[65,101,102]:

"Screening all newborns for a wider number of conditions will lead to an incredible amount of false positives, which may create enormous amounts of follow-up by HCPs."[101]

Non-geneticist healthcare professionals (HCPs) who may come in contact with genetics expressed concern about their ability to understand[15,123]. To address some of these concerns, providing additional training in genetics could promote overall understanding of genetics across other specialties[105]. Such activity would be even more pertinent in the case of WGS-NBS, where communication is vital[105]. In addition to pre-screening counselling, GCs will also need to provide extensive post-screening counselling, which has been perceived as not cost-effective by GCs. Should WGS-NBS become the standard of practice, post-screening counselling will increase in demand, including for asymptomatic children who screen positive. The limited workforce in genetics and the lack of training of other HCPs in genetics was a practical barrier to WGS-NBS[66,69,102].

Discussions amongst several stakeholders were one of the important points suggested by HCPs to address challenges[15,69]:

> *"I don't think it's possible to address (the issues) as one professional group. I think it's a multi-faceted discussion…there are many stakeholders…the lay community…multiple streams of health professionals that would potentially play a role that need to be involved, from pediatrics to obstetrics to genetics, counselors, laboratory, IT."*[15]

One challenge may be to ensure how to engage the public in a meaningful way[66]. GCs could have an important role in the public outreach of WGS-NBS[15].

Proposed practical solutions to including WGS as a first step in the clinics would be targeted screening. That implies sequencing at-risk children who had an abnormal prenatal screening or are not meeting developmental milestones[15]. A targeted screening approach was also suggested as a

compromise that would reduce the amount of VUS and, according to some, a more cautious first step to including WGS in clinics[15].

> *"Families and health care professionals frequently face difficult decisions about the appropriate clinical management of neonates who have profound disabilities, especially when clinicians encounter difficulties in diagnosing these conditions. Before it can provide guidance to decision-making about the clinical management of ill newborns, the diagnostic information that WGS yields first passes through multiple levels of interpretation."* [15]

Finally, there were discussions about storing the data of WGS-NBS[86]. Genetic data is valuable for clinical purposes at birth and can be used in the future by clinicians throughout the patient's lifetime[86] . The "when" to communicate information is critical in the newborn/childhood context: clinicians indicated that the timing of screening/testing should vary depending on disorders; therefore, not everything would need to be screened for at birth.[86] Parents may also have concerns regarding the potential safety and privacy of their child's data, should it be kept after NBS.[130] Public health concerns involve the costs and logistics of storing WGS data[15,28]. If the data is stored, there is a chance that it may be reinterpreted in the future. This presents logistical challenges for HCPs regarding following up with the child later[35].

3.5 EDI and Accessibility

The topics of equity, diversity, inclusion (EDI) and accessibility are becoming more prevalent in literature discussions. They relate to the biomedical ethical principle of justice. In healthcare, EDI can imply ensuring that clinical practices are adapted and accessible to a diverse public. In the NBS context, it could be to provide access to all newborns to the benefits of NBS programs, which is why NBS is already a successful public health program[35]. However, there are inequalities in access to genetic services that stem from different reasons. For instance, genetic research findings are most valuable to individuals with European ancestry. A recent analysis of genetic

studies found that 78% of study participants were of European origin, and minorities remain vastly underrepresented[139]. This leads to biased screening tests that cannot be translated to other populations in clinical practice. Disease-cause mutations differ based on ethnicity, geographical location and cultural populations[35]. This impacts the clinical practice of GCs and other HCPs who may need to analyze and deliver results. To enable better interpretation within a diverse population, it was recommended by Friedman et al.:

"Genomic newborn screening programs should, therefore, make population-specific allele frequencies of every gene included in the program publicly available in a freely-accessible database. The functional consequences (benign, pathogenic, or undetermined) of each allele should also be made available, along with the evidence supporting functional interpretations"[35].

There are also gaps in clinical and policy practices in different jurisdictions. For instance, there are no published guidelines in low-and-middle-income countries (LMICs) on genetic counselling and testing for managing mutation carriers in hereditary breast cancer. In contrast, breast cancer genetic counselling services are well-advanced in high-income countries[140]. Capacity building is also needed so that countries can benefit from research done in their own country, where local experts understand their health[141].

One of the papers identified in the literature was from Bulgaria, and it brought to light some of the barriers to EDI in WGS-NBS. For example, they suggest that small countries might not have the infrastructure and resources that a larger government does to offer such services[123]. Financial barriers remain despite the decrease in cost in WGS. One of the other articles identified through this review discussed two cases and was aware of the privilege of these cases:

"The two cases presented describe individuals who had access to healthcare, providers who informed them of prenatal carrier screening, and referrals to the appropriate specialists for follow-up. Not all people have access to these services for various reasons including location and cost of healthcare." [69]

Furthermore, the literature also emphasized the importance of including minorities to ensure they benefit from WGS-NBS:

…the point is to ensure that you're not leaving behind any groups and that all groups, particularly Aboriginal (and) Torres Strait Islander…are appropriately engaged and involved in the development and implementing programs in their communities."[15]

However, simply making WGS-NBS accessible to everyone may not be enough. Access to follow-up and treatment is necessary to ensure that WGS-NBS programs stay meaningful and fair[66]. For example, sickle cell diseases tend to affect Black individuals, while cystic fibrosis predominantly affects White individuals[142]. Both disorders are included in most NBS programs in the US. However, cystic fibrosis has much more treatment and better health outcomes[142]. In addition to the biases in tests, treatment, and interventions available, there is also systemic racism that influence health outcome based on your sociodemographic status[143]. These are concerning issues that will also impact the delivery of WGS-NBS in the future, which require further thought and research.

Finally, in a study with HCPs in Australia, 84% indicated that ensuring access to existing treatment for individuals who screen and test positive is necessary before implementing WGS-NBS[67]. Finally, some believed that incorporating genetics into NBS would be beneficial due to its universal nature, enabling all to benefit from medical genetics[101].

Chapter 4: Results- The Ethical Duties of Genetic Counsellors

This chapter presents the role and duties of GCs in Canada from an ethical standpoint. These were uncovered from normative ethics documents, such as the CAGC's Code of Ethics, the Knowledge-Based and Practice-Based competencies, and the literature identified in the search described in Section 2.2.4. It presents the role of GCs based on their ethical duties rather than from a practical standpoint. It describes the role of GCs within the traditional healthcare setting who have direct contact with patients, as their role within industry or research is beyond the scope of this thesis. The impact of WGS-NBS on the ethical and legal duties of GCs will be discussed in depth in the discussion Chapter 5.

4.1 Canadian Genetic Counsellors

GCs are certified health care providers "*with expertise in discussing the complexities of genetic screening and testing with families*"[1]. Their scope of practice may vary with the jurisdiction, institution, and position[70]. GCs assist patients in the screening and diagnosis process, interpret results of genetic tests and guide individuals and their families to make informed medical and personal decisions[70,88,89]. They are part of a healthcare team with other HCPs, researchers and scientists involved in providing genetic services[88]. They may be involved in triaging the requests for consultation, preparing and coordinating consultations with medical geneticists, and sometimes they offer genetic expertise counselling to non-genetics physicians[70]. They may work closely with medical geneticists or as part of a team within pediatrics, oncology and other specialties[144].

Genetic counselling was recognized as an independent vocation in the 1960s, following the increased demand to counsel patients in genetics[145,146]. MGs and nurses were previously the ones delivering genetic counselling to patients. The number of GCs is continuously increasing. They

have taken an important place in medical genetics[144]. Today, they also practice outside of the traditional hospital/clinical role, such as in laboratories and private companies[146]. Over the last decade, the role of GCs has become more global, with estimates suggesting that they now practice in approximately 28 countries[146].

In Canada, GCs are certified through an examination, which they may take after a two-year master's program[118,148]. The exam from the American Board is also accepted to practice in Canada[88]. GCs in Canada are encouraged to belong to the Canadian Association of Genetic Counsellors (CAGC)[117], and certain provinces have their own associations[149–151]. The CAGC manages standards of practice, guidelines, position statements and normative documents. The Canadian Board of Genetic Counsellors (CBGC) is responsible for the certification exams in Canada, with the mission of public protection at the heart of the organization[152].

Professions are usually regulated to protect the public from the risk of harm[119,148]. Genetic counselling is not a formally recognized profession in Canada, except for Manitoba[147,153]. In this province, the role is recognized through delegation, where the physician (usually an MG) delegates a *reserved act* to a GC[154]. For example, communicating the diagnosis of a genetic disease may be delegated from the physician to the GC[89,144]. The lack of clarity surrounding the scope of the practice of GCs may impact the ability of GCs to practice autonomously. Professionalization is a recurrent discussion topic amongst Canadian GCs, as the lack of consistency across provinces may impact the care provided to patients[147,148]. Standardizing the profession in Canada is imperative with the increased demand for genetic services[88]. In the US, most states have already recognized the profession and require licensing to practice. As the role expands globally, regulation of the profession is also being considered or implemented in several countries[146].

Canadian GCs are held to specific standards and principles based on their Code of Ethics. A Code of Ethics guides a professional through the *goals and values of the profession*[155]. The code of ethics alludes to the principles of biomedical ethics, such as autonomy, beneficence, non-maleficence and justice[156]. The document was composed using an *Ethic of care* perspective, which is an ethical theory that emphasizes the role of relationships in the moral processing of individuals[157]. It was last updated in 2006. The code of ethics for Canadian GCs is organized into four categories of duties: towards themselves, their patients, society, and their colleagues[117]. Therefore, to describe GC's role and duties toward the patient, the following sections describe each of these relationships.

4.1.1 Duties toward Patients

In their duties with patients, GCs must respect the patient's autonomy, welfare, and freedom[155]. The best interest of the patient should be their primary concern. In their code of ethics, they must understand and respect an individual's capacity to weigh the advantages and disadvantages of the genetic tests available and make informed decisions for themselves[155]. They support their patients in decision-making that promotes informed consent upon the possibility of genetic screening/testing. As part of their relationship with the patient, they also aim to provide suitable clinical and psychosocial assistance, advocate, and make referrals to other professionals as needed[155]. They treat patients with dignity and compassion, respect their confidentiality and have special attention to vulnerable patients[155].

In *La responsabilité civile du conseiller en génétique au Québec*[89], the author suggests that the responsibilities of GCs could be viewed as legal duties toward their patient in Quebec. They are the Duty of Competence, the Duty to Inform and the Duty of Confidentiality. The Duty of

Competence suggests that GCs act in their patient's best interest and recognize their limits in providing care. As part of their Duty to Inform, GCs must promote patients' autonomy by fostering informed consent. For example, they have the Duty to Inform patients of their risk of having a child with a specific condition before conception. The Duty to Inform incorporates the responsibility of counselling in a non-directive manner. Finally, the Duty of Confidentiality originates from the right to privacy, which in Quebec is in the *Code Civil du Québec.* They are not held accountable by the "professional secrecy," as genetic counselling is not a recognized profession held accountable by the *Code des Professions.* The Duty to Inform may conflict with the Duty of Confidentiality when it comes to warning a patient's family members regarding a hereditary condition. This particular case is not addressed in the *Code of Ethics* for GCs. The author of the chapter suggests that GCs may follow similar guidelines as the MGs, who have the *Code de déontologie des Médecins,* and suggests that confidential information may be revealed if health or security risks for the patient or their family. In that way, it stays at the discretion of the doctor (or GC) to disclose such information.

In their competencies, they must meet standards in counselling and communication. GCs must have communication abilities that are adaptable to the patient's needs and respects their integrity and values. They must have techniques to be able to identify their needs and their coping abilities. They must also understand how diversity impacts their interactions. Finally, they must convey and synthesize information that matches the genetic literacy of the patient[88]. Education and research should be part of their roles to ensure to up to date care delivery to patients[88].

4.1.2 Duties toward Colleagues

GC's relationship with colleagues should be based on respect, collaboration, caring and support[155]. As part of their professionalism and ethical practiced based competencies, GCs must effectively work within multidisciplinary teams. They represent a source of genetic information to their colleagues. They also promote competence and accountability among their peers by requesting advice from their colleagues or the ethics team if concerned about other colleagues' behaviours. Finally, they promote mentorship, collaboration and education between genetic and non-genetic colleagues[155]. GCs can take leadership to support growth within the health care team[88].

The working relationship between a GC and MG is close within the health care team. The Duty of Competence includes that they must respect the current legislation, such as not performing *reserved acts* (except for Manitoba)[153].

4.1.3 Duties toward Themselves

In their relationship with themselves, it is expected of GCs to maintain integrity, demonstrate competence, and recognize their limits[155]. They should continue education, be able to self-evaluate and must value self-care for themselves[155]. Their relationship with themselves relates to their Duty of Competence.

According to the knowledge-based competencies document, the scope of practice of GCs is constantly changing concurrently with the developments of the field of medical genetics[118]. The nine areas of knowledge of GCs are *Epidemiology, Population, Basic Human Genetics*, *Clinical Genetics*, *Molecular Genetics*, *Cytogenetics*, *Biochemical Genetics*, *Cancer Genetics*, *Genetic Screening*, *Prenatal Diagnosis* and *Genetic Counselling.*

Noteworthy for the purpose of this thesis, which is on NBS, the genetic screening competencies include:

"7.1 Understand the different types of screening programs, their target population and methodologies. Examples include but are not limited to ***newborn****, prenatal, and population screening.*
7.2 Understand the criteria used to select conditions and establish screening programs.
7.3 Understand the statistical measures of a screening test. Examples include but are not limited to validity, reliability, sensitivity and specificity.
7.4 Understand the risks, limitation and benefits of screening programs including potential ethical and legal concerns"[118].

In their genetic counselling competencies, they must be able to apply their knowledge of client-centred counselling and communication. They must apply effective strategies such as "*contracting, shared decision-making and self-disclosure"*[118]. The three main practical competencies of GCs are in counselling and communication, professional and ethical practice, and genetic expertise, according to the CAGC'S *Practice Based Competencies for Canadian Genetic Counsellors*[88]. One of the initial assumptions in the document is that the role of GCs will continue to evolve with the development of biology and technology. Therefore, the competencies can be revised regularly.

GCs must understand and integrate the theory of genetic counselling models, research, standards and guidelines in a responsible manner[88]. They must demonstrate critical thinking in everyday practice, such as when evaluating data or reviewing the literature. They must show their abilities in clinical case management within a healthcare team. They must continue their professional growth while recognizing limitations as part of their professionalism and ethical competencies. Their practice must align with ethical and legal principles while identifying their values and biases[88].

4.1.4 Duties towards Society

In their relationship with society, GCs must promote the well-being of people and access to genetic services and health care[155]. They must also promote diversity, provide non-judgmental psychosocial support, and stay well-informed about the research in the field[155]. As a GC, it is crucial to display respect towards all individuals, irrespective of their race, religion, sexual preference, gender, ability, or socio-economic and genetic background[155].

GCs, as part of their duties towards society, raise awareness about the work of their profession by participating in multidisciplinary teams, educating the public, contributing to policy-making, and consulting at the provincial/national level[117]. They must show professionalism and ethical practice as part of their practice-based competencies. They may also advocate for their patients, especially those considered vulnerable[88].

Chapter 5: Discussion

5.1 Genetic Counselling in the WGS-NBS Context

There is a surge of interest in integrating genetics into clinic screening and diagnosing procedures. Several stakeholders, such as patients, parents, researchers, and clinicians, have shown interest in expanding NBS programs with sequencing[67,87,103]. Unquestionably, WGS-NBS can be beneficial, enabling monitoring and early treatment of conditions and reducing the diagnostic odyssey lived by parents. WGS newborns can be empowering for parents, as it grants them the ability to prepare, take proactive measures and understand to a certain extent, the postnatal needs of their child. It can also be of help for future pregnancies and family planning. For the child, it may give them access to follow-up, improve their quality of life, and even save their lives. For a public health care system, WGS may become cost-effective in the future, reducing the costs of various testing and appointments before diagnosis, improving medical management of patients and reducing the costs of expensive hospitalizations and measures if preventive measures/treatments are already available. Standard NBS, at its core, is justified by the best interest of the child standard. However, WGS has also raised concerns for its feasibility, utility, potential long-term harm to the child, privacy, and other ethical issues, as shown in Chapter 3. Thus, as with any biotechnology, it must be responsibly integrated into clinical care. How can policies be developed that ensure an ethical implementation of genomics into clinical care?

In line with the child's best interest, children have the right to health and to benefit from the progress of science[71]while balancing the potential harms that could compromise other aspects of their lives. At present, only certain conditions are screened for at the birth of a newborn, with the expectation that supplementary conditions will be added through research and development of

screening/diagnosis tests and treatments[76]. For instance, a broader scope of results could be screened for using WGS. The pilot projects in the UK and the US are screening for additional conditions. In contemplation of this potential future, how will GCs respond and address such ethical and policy concerns? What are their roles and moral duties in this context? The literature suggests that GCs will play a critical role in the future of NBS should WGS become the standard of care[15,64,69]. It is known that the practice of GCs in clinics adds significant value to the services provided to patients with genetic conditions and their families[96,158]. It is, therefore, essential to understand how GCs will face ethical and policy issues in WGS-NBS.

The following section explores the themes revealed in Chapter 3 and the duties identified in Chapter 4 and compares how they fare with each other. The five main themes identified through the literature review were 1) the challenges in interpreting, managing, and communicating results; 2) the challenges in informed consent; 3) psychosocial and long-term risks 4) the practical challenges and finally, 5) the EDI and accessibility concerns. Section 5.1 presents the four relationships that GCs have according to their Code of Ethics (with patients, colleagues, themselves, and society) and discusses how these ethical issues might impact these relationships. Section 5.2 draws points to consider for WGS-NBS. Section 5.3 discuss the future directions of this research.

5.1.1 Patients

The Duty to Inform is the first topic related to GCs' responsibilities toward patients. How can GCs foster informed consent in the WGS-NBS context? GCs will navigate a situation of stress and vulnerability for parents that can impact their decision-making. Although GCs empower parents to make informed decisions and guide them through complex genetics concepts[76], their work cannot ensure that informed consent is fully achieved. The complexity of WGS may challenge

their Duty to Inform. For example, parents who receive a negative screening might not understand the whole meaning of the results: it is not because there are no apparent genetic anomalies that the child may not have or develop other conditions. As previously discussed, it may also be that conditions are not reported back to the family because they do not meet the criteria to be included in the screening, or there are simply VUS that were not reported back. Finally, even when the screening turns out to be a false positive, parents seem to believe their child still has a condition or was sick, which may lead to the medicalization of the child[129]. Therefore, WGS-NBS might require an extensive pre-screening counselling session for the parents[76,159], which is not a procedure currently available in regular NBS programs[65]. Pre-counselling does not only promote informed consent but could manage parents' expectations towards NBS[160]. It could also enable customizable screening, with opt-in choices for parents about which conditions they wish to know[120]. Additionally, before the child's birth, counselling and preparation could be provided in the pre-natal stage to reduce the burden of information on the parents at birth[161].

The literature review also emphasized the need for and importance of long-term counselling. Family Centered Care could be used to ensure the best care possible in the short and long-term run[162] , as its goal is to create the environment for discussion within families for hereditary conditions. Increased communication between different HCPs would also be required for a more holistic approach to the health care of newborns and their families[162]. Furthermore, telehealth services have been shown to overcome some barriers to service access. It reduced costs and wait times while being a satisfactory method for patients[70]. Telehealth could promote access to long-term counselling. Figure 3 is an original figure describing the different stages of counselling and consent for a family whose newborn has screened and been diagnosed positive:

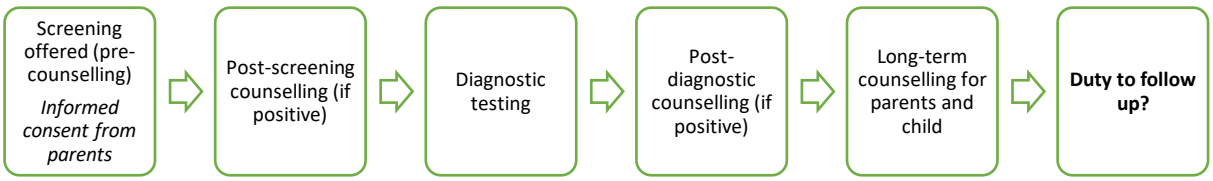

Figure 3: The consent and counselling process in WGS-NBS

As the newborn becomes a child, adolescent, and adult, they will continue to require support in the long-term with their genetic condition. With the emergence of WGS-NBS, it may be necessary for GCs to undertake an additional obligation referred to as *the Duty to Follow-up* to support their patients (i.e. last box in Figure 3)[163]. The Duty to Follow-up is currently the physician's legal duty: once they offer care to a patient, they become responsible to following-up[164]. They may not abandon the patient on his own[164]. This duty ends when the medical contract ends: when the patient's condition is taken into charge by another physician, if the patient wishes to end the care, for personal reasons of the physician (e.g. retiring) or if the patient is healed[164]. If WGS was offered at a population level, there might be a need to include this duty for other HCPs, such as GCs. Therefore, GCs could become ethically responsible for this long-term follow-up through this duty. Alternatively, this may remain a duty restricted to the practice of physicians, which already have the responsibility to follow up. The Duty to Follow-up poses several practical and logistical challenges, such as families relocating and potentially losing contact with the hospital. Furthermore, this duty may imply releasing additional WGS results at different times than at birth[86]. Therefore, it requires further consideration and thought.

The complexity of WGS may also impact informed consent. Public literacy on genetics is limited. If it can already be challenging for HCPs to grasp, interpret and communicate WGS results and know its consequences, as was shown in section 3.1, it may be even more difficult for parents.

Consent would be even more limited in a context of high stress, increased uncertainty, and vulnerability as new parents, compromising proper informed consent. To overcome such issues, the literature demonstrated that GCs could contribute to developing online and educational tools for parents. Patients, in general, already use the internet extensively to understand and inform themselves about conditions, which can even impact their decision-making[165]. Parents might also be involved in support groups and other online communities where they exchange information with each other[166]. The internet and other sources can lead to misinformation, as it was shown to be highly disseminated with vaccination information[167,168]. In this case, a GC's role would be to promote educated use of the internet by suggesting reliable sources and tools that the parents may access or how to find reliable internet online. The traditional patient-provider relationship changed as internet-informed patients felt more empowered and communicated better with their HCP[169]. The need for the development of educational tools has already been acknowledged by genetic counselors in Canada as a priority for patient care. As part of the GenCOUNSEL project in Canada[170], the DECIDE online tool was developed to help parents understand and process information at their own pace[171]. The development of a personalized genomics results e-booklet has also been shown to help families and facilitate communication[172]. Finally, GCs could advocate by supporting or recommending national educational campaigns to parents.

The scope of delivering results to parents following WGS remains a subject of debate due to the potential stress experienced by parents and the potential psychosocial consequences for the child. Approaching the topic from a different standpoint, limiting the information provided to parents because of the possible stress and the uncertainty they may live with may be perceived as a paternalistic approach to NBS. Limiting the information that parents have access to decreases their autonomy and decision-making. In the GUARDIAN study, parents may opt for 100 other

diseases despite no treatment for the disorders[53]. It enables parents to decide if they want to know more information. As mentioned above, this opt-in method promotes their autonomy but must be accompanied by appropriate pre-counselling[67]. The GUARDIAN study also proposes that if the child screens positive, parents may want to consider research studies/clinical trials for specific therapies for their child, raising ethical concerns.

Being screened and identified at birth would make parents more aware of clinical trials available for their children, which would be incredibly beneficial to the child. It would also promote children's right to benefit from the progress of sciences. However, it conflicts with their children's autonomy, as they cannot choose to participate in research studies. They might be exposed to the potential risks of a clinical trial, which in some cases, could be balanced by the consequences of inaction. Considering the long-term effects, research participants must test and validate new treatments, which could benefit future children in the long run. The relationship between NBS programs and research is complex and requires its analysis, which falls outside the scope of this thesis. Still, GCs within the health care clinical setting could face such issues. In the case of the family of a child who screens positive and is confirmed with diagnostic tests, GCs would have the opportunity to disclose clinical trials/research projects available as potential courses of action for parents. As part of their duties in their code of ethics, they must recognize and respect parents' ability to understand the benefits and risks of services being offered and ultimately respect their decision. At the same time, it may conflict with the duty to ensure that vulnerable patients are treated with due care. In the WGS/NBS context, transparency from such programs is vital for families to understand what is and is not included and why. This might reduce paternalistic practices while promoting trust between the parents and patients.

Finally, the Duty to Inform may conflict with the Duty of Confidentiality when it comes to warning the family members of the newborn regarding a hereditary condition. Parents receive actionable carrier status results in the BabySeq project that used WES in newborns. Carrier status is a highly debated topic in the literature[173]. Should WGS-NBS become a reality, GCs would need clear guidelines on information disclosure to parents, including carrier status. Disclosing results that may be beneficial to the parents but not directly beneficial to the child remains a debate within the community and is not discussed in their Code of Ethics[155]. The approach in the US has been to promote parents' preferences and decision-making in pursuing carrier screening[174]. In Canada, the previous guidelines from 2016 on carrier screening were withdrawn[175] , and the CCMG is currently working on new approaches to carrier screening in clinical practice through the *CCMG Reproductive Carrier Screening Ad Hoc Working Group*[176].

5.1.2 Colleagues

A recurrent theme across the literature, as described in section 3.4, was the unmet need for genetic services. WGS-NBS would lead to additional children requiring follow-up, which could strain an already overburdened healthcare system. In Canada, it will likely be impossible for solely genetic specialists (GCs and MGs) to respond to all the care needed for newborn genetic screening. Workforce analysis confirms that capacity building and the need to train other HCPs in genetics are evident[70]. For example, as primary care physicians' training and knowledge in genetics vary, they often feel they lack the knowledge and expertise to deliver genetic counselling[177]. Pediatricians, in particular, are important stakeholders involved in caring for newborns and potentially exposed to various genetic conditions[123].

In their duties towards colleagues, GCs are a source of genetic information to their colleagues and can take leadership positions and promote education within the health care team[155]. Thus, as proposed in the results, they could provide training and support in genetics to other HCPs who do not have genetics training or expertise yet might be involved in WGS-NBS[155]. This collaborative approach can enhance the overall knowledge of genetics within the healthcare team. With the limited number of genetic specialists available, nurses might be, for example, appointed to perform pre-screening counselling, and it would be vital for them to also receive training in genetics beforehand. The need to promote genetics education within the clinics has been recognized in Canada. The Genetics Education Canada: Knowledge Organization (GECKO) is a program that aims to raise awareness of genetics in the clinics, developing resources for clinicians and for the public[178].

The regulation of the GCs in Canada can play a pivotal role in enabling GCs to practice at the top of the scope of expertise, addressing some of the limitations to access to care. Professional regulation can empower GCs to work autonomously within clinical settings, thereby increasing access to care. It would create a better definition of the scope of practice of GCs, a critical step in enabling them to practice at the top of their scope and increase access to patient care while reducing the risk of harm for patients [70,148,179]. The delegation model, where the physician delegates an act to a GC, might only meet some of the needs required for WGS-NBS. This is because the delegation model requires a constant supervisor delegating act[153], which may not always be possible in a population-level screening (especially when a non-geneticist does the delegation).

Furthermore, to promote increased access to care, Genetic Counsellor Assistants (GCAs), which are currently more present in the US, could be used as a model to reduce the administrative burden of GCs and enable them to practice at the "top of scope"[180]. GCAs perform administrative

tasks and may contact patients to collect information or disclose negative results. They have been shown to increase efficiency, where more patients could be seen, and the cost per patient was significantly decreased[179,180].

5.1.3 Themselves

GCs' duties towards themselves relate to their competencies and their values. GCs must stay knowledgeable of the latest research as part of their Duty of Competence. The Knowledge-based competencies document described GC's role within screening programs, highlighted in section 4.3. It describes the basic requirements to understand screening programs and apply to NBS. However, interpreting results from WGS can be particularly difficult not because of the capacity of HCPs but rather the lack of knowledge we have in general concerning genotype-phenotype relationships, as well as VUS. Thus, to maintain competence, there is a clear need for new guidelines and policies to guide GCs in clinical practice.

There is a movement in academia to include the voices of patients and other stakeholders in developing research, policies and guidelines. The literature suggested that the representatives of various stakeholders are needed to make policy decisions in the complex case of NBS[63,67]. Patients have shared that their voices may significantly impact setting the attitude and developing policies[126]. As a point to consider, I propose the development of communities of practice to solve some of the ethical and policy issues that GCs might face. A community of practice is defined as "*a group of people that share a common concern and who come together to fulfill both individual and group goals."* It enables various group members to contribute and participate in critical inquiry[181]. This model has been discussed as a possible way of involving communities in the research cycle and governance frameworks. This case would involve GCs, MGs, nurses, pediatricians, parents and other stakeholders. This has been previously done in the past, where

Skirton et al. demonstrated how a community of practice was developed and led to the development of standards of practice for GCs in Europe[182]. It also enabled them to define the profession and role of GCs within Europe and to develop a code of practice.

In Canada, efforts are currently in place such as the CAGC who currently organizes a community of practices for their members for the development of standards of practice [183]. Creating a larger community of practice that involves other HCPs could help promote knowledge within the newborn care team. This model could be used to promote involvement of different HCPs, including those who are not specialized in genetics, in the current issues of genetics that might affect their patients. To proceed, a feasibility assessment would need to be done in Canada, taking into account the unique context of each province.

The community of practice model should also include those who represent vulnerable populations. Jordan's principle was mentioned in the land acknowledgement section of the thesis. It is an Indigenous principle to ensure healthcare access for all children. It is based on the story of Jordan River Anderson, a Norway House Cree Nation child born with several disabilities. The federal and provincial governments discussed who would pay for his at-home care for several years [184]. Canada's difficult history with Indigenous communities has heavily impacted the health of Indigenous communities[185]. Indigenous People are 5% of the total Canadian population[186] , and the challenges surrounding their access to healthcare must be discussed, particularly in the face of WGS-NBS, a public healthcare program. One step, for example, would be to include representatives of Indigenous People in the community of practice. It would enable addressing questions about reducing health gaps and involving them in policy and decision-making. Creating trust and rapport may be challenging at the policymaking level and in the patient-GC relationship. A guide for genetic counselling in indigenous communities has been developed as part of the *Silent*

Genome Project[187]. It recognizes GCs' role in providing culturally safe counselling to such communities. It calls on principles of transparency, humility, partnership, flexibility, self-determination, and accountability to guide the counselling provided.

Furthermore, Vockley et al., in a recent article[188], highlight that using gene therapies is an essential change in the clinical management of conditions. However, the role of MGs within this has not been clarified yet. In Europe and the US, gene therapy is not seen as a core competency within the training of MGs[188]. However, HCPs must promote access to treatment or therapy if we screen newborns for treatable disorders. Therefore, this thesis proposes that GCs could also include competencies and knowledge in new therapies as part of their training. Gene therapy or knowledge in treatment is not discussed in the Competencies documents of GCs. Therapeutic interventions are mentioned in the "Public Health and Advocacy" section: *(GCs) demonstrate an awareness of resource allocation and cost-effectiveness in making decisions related to relevant diagnostics and therapeutic interventions*[88].

The ability to treat medical conditions for patients who screen positive is a fundamental principle of NBS. GCs may benefit from further development of their skills and expertise, which could include training in new therapies such as gene therapy. If GCs are knowledgeable about the availability of treatments, they may, in their turn, inform parents of the possible treatments available. It would be necessary for their knowledge or practice competencies to be updated to include such topics, especially with the advent of gene therapy and other technologies.

5.1.4 Society

Within society, GCs must foster the well-being of individuals and promote equitable access to genetic services and health care. In the face of potential psychological harm through stigmatization

of the child, do GCs have a role to play? Preventing the potential psychosocial harm to the child relates to nonmaleficence, one of the basic bioethics principles and duties of an HCP[69]. In their code of ethics, GCs "*have a particular responsibility to ensure vulnerable patients are treated with due care."* Newborns are considered vulnerable patients due to their inability to consent. The potential psychological, stigmatization and discrimination risks must be something that GCs can understand and potentially mitigate. The literature review identified one article *"Whole-Genome Sequencing and Disability in the NICU: Exploring Practical and Ethical Challenges."* that emphasized GCs' role in advocating for care for children with disability and reframing disability within the medical institutions. They can contribute to knowledge dissemination and new ways of looking at disability in a social context, for example, promoting the concept of neurodiversity, which embraces diversity and encourages society to perceive brain differences as normal variations within a population rather than incapacities[189]. Being neurodivergent is defined as experiencing and interacting with the world in a divergent way, such as in the case of individuals with an autism spectrum disorder[189]. In this model, society adapts to the needs of individuals, rather than the other way.

Simultaneously, a public health-care system that implements genetics into NBS would naturally contribute to the *destigmatization* of genetics and what having a genetic disease truly entails. The natural genetic variability within the population would be further exposed with WGS-NBS. This could perhaps reduce the notion of genetic determinism, a term describing how the role of genetics is overemphasized in its importance in shaping health and identity[190]. If all newborns were screened and found to have several variabilities in genetic variants and variations in phenotype penetrance, it could challenge the concept of genetic determinism within societies. Counselling is a process that can aid in the destigmatizing conditions[191]. In the case of newborns,

it could reduce children feeling stigmatize by a diagnosis of a genetic conditions as well as carrier status[192].

Another theme that relates to GCs' relationship with society is accessibility. Ideally, equitable access to the benefits of medical genetics should be ensured for all community members. However, entrenched inequalities in health care systems limit access to these benefits to more vulnerable populations. Statistics illustrate this: every year, 6% of all newborns worldwide are born with a severe congenital disability, and 94% occur in LMICs[193]. Globally, there are gaps in financial resources, educational resources, and access to health care, including genetic counselling. Genetic counselling remains primarily available in North American and European countries[194]. It is estimated that there are only 7000 GCs worldwide, with a concentration mainly in North America and Europe in urban areas[146]. Although genetic technologies are becoming more available in LMICs, genetic counselling remains scarce. Yet, genetic counselling is crucial to the responsible integration of gene technology into the health care system[194–196]. Without this service, there could be harm caused by a lack of information, misinformation, and psychological stress that GCs could typically provide support and manage. The lack of access to genetic counselling services can limit the ability to make informed decisions and understand their implications[197]. For Indigenous people, access can be even more restricted and difficult due to a history of distrust and a lack of access to health care services given social and geographic restrictions[185,198]. The systemic barriers that Indigenous communities face to access healthcare require further reflection in the case of future use of genetics in NBS. This topic expands to populations in rural areas as well as other populations within Canada who are more likely to face health inequities, including immigrants, sexual and racial minorities, and people living with functional limitations[199].

What are GCs' duties concerning EDI and accessibility? As presented in Chapter 1, there is variability in access to genetic counselling and the number of conditions screened (14-36) within Canada[19]. Before implementing WGS-NBS, accessibility to GCs and access to care and treatments may be discussed nationally. To begin reducing the health gaps, GCs should possess a thorough comprehension of the challenges related to equity, diversity, and inclusivity in the utilization of WGS-NBS. It is crucial for them to integrate this knowledge into their daily practice and advocate for minorities or vulnerable populations. This relates to their responsibility and special attention towards vulnerable patients.

Finally, within the EDI context, WGS-NBS is embedded in a social, cultural, and sometimes religious context. How do these factors influence genetic counselling? This was not discussed in the literature identified, yet it may impact the care delivered. For example, Indigenous people are more likely to involve family or community members in decision-making[114,187], which could affect their option to perform WGS-NBS. They may also have different views on what health and wellness means and have their coping strategies[187].

Since genetics is not part of any public health program at the moment, we do not know precisely how the social, cultural, and religious factors would play a role in WGS-NBS, especially in Canada, which has a diverse population. In the code of ethics of GCs, they must be aware of culturally diverse practices and support patients non-judgmentally. Expanding NBS could require additional support for GCs, as they would be more exposed to various cultural encounters. The *Silent Genome Project*[187]'s counselling guide, discussed above, discusses how Indigenous People might approach contracting and taking pedigrees. It might have a role for other collectivist cultures. Yet, perhaps more research is required on these factors' part in WGS-NBS.

5.2 Proposed Points to Consider

During the discussion, this study reflected on various ethical issues and assessed their potential impact on the ethical responsibilities of GCs in Canada in the case of WGS-NBS. This section will enumerate points to consider summarizing the findings and reflections above. They target GCs and the community involved in delivering newborn screening services in the future. The points to consider have been created within the constraints of the methodology of this thesis. Thus, they discuss only specific themes that were identified through the thematic analysis and how they fare with the duties identified in the ethical normative documents. These points to consider are proposals that require further stakeholder engagement, research, and validation. They aim to raise awareness of specific ethical issues in WGS-NBS and how they may impact the future of genetic counselling in Canada. In congruence with the discussion, the points to consider were separated by duties toward patients, colleagues, themselves, and society.

Table 3: Points to Consider for Canadian Genetic Counsellors in the WGS-NBS Context

Patients
• Before conducting WGS-NBS, it is important to provide pre-counselling to parents to explain the process of WGS and screening, with its benefits and risks. Although pre-counselling is not currently a standard practice in NBS programs, it may be necessary to ensure informed consent and manage parents' expectations with regards to sequencing. This would involve the development of clinical guidelines for pre-NBS counselling procedures for GCs. • In the context of pre-counseling, giving parents the choice to choose to screen for certain conditions through WGS-NBS can enhance their autonomy. However, it is vital to evaluate the practicality of this option in clinical settings, the genetic counseling necessary, and the possible effects on the child and family.

- The diagnostic odyssey is a continuum that requires long-term support. This requires new communications approaches in genetic counselling, such as Family Centered Care and telehealth. This would require an assessment of the suitability of GCs being part of this type of long-term care.
- WGS generates a substantial amount of data that may pose a challenge for parents to fully comprehend. In the context of NBS, where all newborns would receive this care, it is essential to enhance access to genetic information for the public. GCs can play a crucial role in developing educational resources that promote informed consent and genetic literacy among the public. Additionally, they can offer pre- and post-screening support and guide patients toward trustworthy resources to mitigate the risk of misinformation in WGS-NBS.
- In the light of the discussion about potentially returning carrier status using WGS, it will be important to convey to patients the ramifications on the information being discovered on relatives. GCs duties towards the patient and relatives in this context requires further discussion. It may be beneficial to explore the possibility of establishing guidelines that could aid GCs in this context.

Colleagues

- The use WGS will largely increase the need for genetic support within NBS programs. Further collaboration between non-genetics and genetics specialists, such as GCs, may be required to develop new standards of practice. For example, the consent process in NBS may need to be revisited.
- In Canada, genetic counselling is a service that is already in high demand and has long waiting lists. The implementation of WGS-NBS will put additional pressure on the limited resources available. Further research is necessary to identify potential solutions to alleviate this issue. An avenue might be to regulate the profession to ensure that they can practice autonomously and at top of their scope. To reduce the administrative workload of the medical genetics teams and improve patient access to care, genetic counsellor assistants as support may be a viable option.

Themselves

- Genetic counselling is an interdisciplinary field that is constantly evolving. WGS-NBS will require new standards of practice such as in interpreting, managing**,** and communicating results. It would be beneficial to establish standards of practice and guidelines through communities of practice. This would involve, to the extent possible, include critical stakeholders such as GCs, MGs, pediatricians, rare disease patients and representatives of other communities. This approach can help delineate responsibilities, competencies and emphasize complementarity of roles.
- In the advent of WGS-NBS, GCs may need to update their knowledge and competencies. For example, they may receive further training in available therapies, such as gene therapies.

Society

- Access to equitable genetic counselling is essential to a fair and responsible WGS-NBS programs. GCs should possess a comprehensive understanding of the issues surrounding equity, diversity, and inclusivity in the use of WGS-NBS, and incorporate this knowledge into their everyday practice. This could involve the development of culturally appropriate counselling tools or educational tools in different languages.
- The use of WGS will likely lead to more diagnostic odysseys, including for asymptomatic children. In that context, GC's need to be cognizant of reducing the stigma and discrimination associated with disability. They can advocate for the accessibility of services to children with disabilities. They can also play a role in reframing disability within medical institutions. Reducing the stigma and discrimination related to disabilities can begin at how we introduce them to families.

5.3 Future Directions

The proposed points to consider are preliminary suggestions for future GCs counselling patients and families who undergo WGS-NBS. However, these proposals require feasibility and validity assessment. For example, further research is needed on the benefits and practicality of pre-

counselling, long-term counselling, and the duty to follow-up. Furthermore, the impact of receiving carrier status through WGS-NBS would also require a feasibility assessment and analysis of the impact on families and children. In order to better understand the needs and challenges faced and that might arise for GCs in this context particular, it is necessary to conduct interviews and further engage with the community. Within the Canadian context, more discussions surrounding the topic of WGS and NBS are required to understand its feasibility and barriers,

In this thesis, the role of GCs was discussed only within the healthcare system. However, their role within research could also be investigated. All GCs have contact with research as it is a mandatory training program component[114]. Sometimes, they work dual roles in clinics and research or laboratories. The points to consider could also be explored within the research setting. For example, GCs can advocate for greater EDI in research. This could result in the development of more accurate screening tests for minorities. Promoting EDI in research would translate into better clinical care for other populations. GCs can also take part in researching the potential long-term psychological impacts on children and parents that may arise from sharing genetic information at birth.

Chapter 6: Conclusion

WGS in NBS programs will introduce new ethical and practical intricacies to the clinics. GCs constantly face new ethical challenges as genetics expands in clinical care. Their role in the pre and post-counselling of WGS-NBS in the future is a consensus in the literature[15,64,69,76]. Thus, they will need to navigate the complex ethical landscape of WGS-NBS, and their duties and competencies must be updated accordingly. This research aimed to identify potential ethical challenges GCs might face in the future and discuss how these fare with their current duties. It focused on their duties from an ethical perspective within a Canadian context. The first aim was achieved through a thematic analysis of the ethics literature on WGS and NBS from a clinical standpoint (Chapter 3). The second aim was achieved by first identifying and analyzing the normative policy documents for Canadian GCs to identify their ethical duties (Chapter 4). The third objective was achieved by examining how these duties fare with WGS-NBS and proposing points to consider for future genetic counsellors in Canada (Chapter 5).

As part of their relationship with patients, GCs may provide pre-counselling to promote informed consent in WGS-NBS. They may also be involved in long-term counselling of newborns and their families. GCs could also play a role in developing educational material to help patients reach informed consent and make treatment or other care decisions. As part of their relationship with colleagues, GCs could provide training and support in genetics to other HCPs who are not genetic specialists. The regulation of the profession may also enable them to practice more autonomously and delegate some of the administrative work to GCAs. This can ultimately improve access to care, which is essential in the WGS-NBS context. In their responsibilities to themselves, their competencies could be updated to include treatments such as gene therapy. Their standards of practice or guidelines can be developed through communities of practice. Finally, in their

relationship with society, GCs should have a thorough understanding of equity, diversity, and inclusivity issues related to WGS-NBS. They can play a role in advocating for disability communities and help decrease stigma in the medical institution.

At present, there are various ethical and practical challenges to the integration of WGS-NBS into clinics. Canada's health care system would require further evaluation of the impacts it may have in clinical practice. There are already disparities in NBS across provinces in Canada as the conditions screened vary between 14 to 36. Furthermore, there are provinces and territories with very few or no GCs in Canada[19,153]. This raised equity issues in access, particularly in populations who already face health inequities in the country, such as Indigenous communities[199]. The points to consider are suggestions to answer the clinical needs that WGS-NBS would create but that require further feasibility assessment. Although they have been created within a Canadian context, they could potentially be applied and considered for a more extensive international practice of GCs within the WGS-NBS context.

The NBS program is a successful public healthcare initiative implemented across multiple countries. Its effectiveness and accessibility have strengthened the public's confidence in NBS programs. However, integrating WGS into NBS could present new challenges impacting its inclusivity, credibility, and public trust. HCPs may encounter ethical and practical challenges during clinical practice. Clinical standards and guidelines must be revised for the responsible and ethical integration of WGS-NBS. The responsibilities and duties of GCs must be revised to align with the new requirements. With the WGS-NBS on the horizon, the Canadian genetic counselling community has not only the opportunity to engage in these discussions, but to lead the way and be in the forefront.

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