Clinical implementation of next-generation sequencing technologies in France and Quebec: A multidisciplinary analysis of policy implications.

Gabrielle Bertier

Centre of Genomics and Policy
Department of Human Genetics, Faculty of Medicine
McGill University, Montreal, Canada
-
Inserm UMR 1027, Team 4
Innovation trajectories in health: bioethics issues and public health impact
Université Toulouse III Paul Sabatier, Toulouse, France

A thesis submitted in May 2018:
to McGill University in partial fulfillment of the requirements
of the degree of Doctor of Philosophy
to Toulouse III University Paul Sabatier in partial fulfillment of the requirements of the
Doctorate degree and title of Doctor

ABSTRACT

The decreasing cost of next-generation sequencing (NGS) technologies has resulted in their increased use in research, and in the clinical context. Indeed, the correct interpretation of a human genome can, to some extent, enable better prevention, diagnosis and treatment strategies. Significant public investments in NGS have been made in various developed nations to realise the promise of personalized medicine. Yet, today the sequencing and analysis of a patient's exome or genome is only offered as a clinical test in a limited number of clinics around the world. France and Quebec have made sizable investments in genomics research, and France announced the launch of a genomic medicine plan in 2016. However, policy decisions still have to be made on the nation-wide clinical implementation of NGS technologies in both jurisdictions. Therefore, this project's objective was to contribute to the body of evidence available to policymakers in France and Quebec on the clinical implementation of NGS technologies. We focused our attention on two specific NGS technologies, namely Whole Genome Sequencing (WGS), and Whole Exome Sequencing (WES). We specifically aimed to assess if the responsible and efficient use of WES/WGS data in the context of clinical care could be impeded by policy gaps. Currently, the clinical interpretation of a patient's genome sequence data is done through the intervention of many stakeholders including basic science researchers. These researchers use bioinformatics tools, processes and norms developed for research to filter and analyse patients NGS data. In parallel, existing regulatory and normative frameworks have been developed for the use of genetic data, and include no clear definition of genomic data or genomic technologies. We hypothesised that these elements create a strong need for standardization of practices, and may require adaptations of current regulatory and normative frameworks to the context of NGS.

We therefore aimed to answer three research questions:

(1) What issues do technology users experience and foresee when using WES data to inform patient care? To answer this, we performed a systematic review of the literature.

(2) How are patients' NGS data currently managed (produced, analysed, interpreted and shared) in clinical institutions in Quebec and in France? We answered this by performing a case studies

analysis, interrogating key stakeholders directly involved in managing patients' NGS data in France and Quebec.

(3) Are there gaps in the current regulatory and normative frameworks which should be addressed to enable a responsible and efficient standardized use of NGS data in the clinic? To answer this, we performed a narrative review of the currently applicable normative frameworks in France and in Quebec.

In our systematic literature review, we identified 23 distinct challenges linked to the production, analysis, reporting and sharing of patients' WES data. We also found that technology users were calling for practices to be more standardized before NGS was offered as a clinical test, and that numerous infrastructural adjustments had to be made in order for healthcare institutions to accommodate the vase amounts of highly complex NGS data. Through our case study analysis, we showed that in addition to managing the various levels of complexities of producing, analysing and sharing complex NGS data, a significant buy-in from numerous stakeholders was necessary in order to offer clinical genomics to patients. At the National level, this cannot be done without a strong political will. Finally, through our normative frameworks analysis, we concluded that existing frameworks were highly protective of patients and research participants, and could need marginal adjustments in order to accommodate for NGS tests. However, we also concluded that clinical genomics could not be realized without political will, and sustained monetary and infrastructural investments, which are only partly present at the moment in France and Quebec.

RÉSUMÉ

La chute des prix des technologies de séquençage de nouvelle génération (NGS) s'est accompagnée de leur utilisation accrue, en recherche et en clinique. En effet, l'interprétation toujours meilleure des génomes humains peut permettre le développement de meilleures stratégies de prévention, de diagnostic et de traitement des maladies. Des investissements significatifs ont vu le jour dans de nombreux pays industrialisés en vue de réaliser les promesses de la médecine personnalisée. Cependant, le séquençage et l'analyse du génome complet de patients n'est offert en tant que test clinique que dans un nombre très limité d'établissements de santé dans le monde. La France et le Québec ont investi de manière considérable dans la recherche en génomique, et la France a annoncé en 2016 le lancement d'un plan national de médecine génomique. Cependant, des décisions stratégiques doivent encore être prises quant à l'implémentation clinique des technologies NGS dans ces deux juridictions. Dès lors, l'objectif de ce projet est de contribuer à l'ensemble des preuves et faits à la disposition des décideurs publics en charge du dossier de la médecine génomique. Nous avons focalisé notre attention sur deux technologies en particulier, le séquençage de l'exome (whole-exome sequencing, WES) et du génome complet (whole-genome sequencing, WGS). Plus spécifiquement, notre objectif était d'établir si l'utilisation efficace et responsable du WES/WGS pouvait être mise en péril par des lacunes dans les politiques professionnelles ou publiques ou dans les cadres règlementaires et normatifs applicables. A l'heure actuelle, l'interprétation clinique de la séquence génomique ou exomique d'un patient nécessite l'intervention de nombreuses parties prenantes, y compris des chercheurs scientifiques. Ceux-ci utilisent des outils bioinformatiques, procédés et normes développés dans le cadre de la recherche pour filtrer et analyser les données NGS. En parallèle, les cadres normatifs existants ont été construits pour accommoder les données génétiques, mais n'abordent pas la question des données ou technologies génomiques. Notre hypothèse est que ces éléments créent un besoin important de standardisation, qui pourrait requérir des adaptations du cadre normatif existant. Nous avons donc répondu à trois questions de recherches :

(1) Quels enjeux les utilisateurs de technologies NGS soulèvent-il à propos de leur utilisation en clinique ? Pour répondre à cette question nous avons fait une étude systématique de la littérature.

(2) Comment les données NGS de patients sont-elles gérées (produites, analysées, interprétées et partagées) à l'heure actuelle par des institutions de santé en France et au Québec ? Pour répondre à cette question nous avons réalisé une étude de cas multiples, et interrogé des acteurs clés impliqués dans la gestion de données NGS de patients en France et au Quebec.

(3) Y a-t-il des lacunes dans les cadres normatifs qui devraient être comblées pour assurer l'utilisation responsable, efficace et standardisée des données NGS en clinique ? Pour répondre à cette question nous avons fait une revue narrative des cadres applicables en France et au Quebec.

Dans notre étude systématique de la littérature, nous avons identifié 23 enjeux différents liés à la production, l'analyse, et le retour de résultats de données NGS de patients. Nous avons aussi trouvé que de nombreux utilisateurs des technologies NGS appelaient à ce que les pratiques soient standardisées avant l'introduction de WES/WGS en tant que test clinique. De plus, nombre d'entre eux indiquent que de nombreux ajustements infrastructurels devront être fait pour que des institutions de santé puissent accommoder le stockage, et l'interprétation de données massives et complexes en génomique. A travers notre étude de cas multiples, nous avons découvert qu'en plus de la gestion de nombreux niveaux de complexité des données NGS, il est nécessaire d'obtenir l'appui de nombreuses parties-prenantes avant de pouvoir offrir le WES/WGS aux patients. Organiser cela à l'échelle nationale ne peut pas se faire sans une volonté et engagement politique fort aux plus hauts niveaux de l'Etat. Enfin, notre étude des cadres normatifs applicables a montré qu'ils étaient très protecteurs des patients et participants à la recherche, et pourraient nécessiter des ajustements mineurs pour accommoder les tests génomiques. En revanche, nous avons aussi pu conclure que la médecine génomique ne pourrait pas être mise en place sans un engagement politique, ainsi que des investissements monétaires et infrastructurels forts, qui ne sont que partiellement présents actuellement en France et au Québec.

TABLE OF CONTENT

LIST OF ABBREVIATIONS

ABM: Agence de la Biomédecine

ACMG: The American College of Medical Genetics and Genomics

ARS: Agence Régionale de Santé

Aviesan: Agence Nationale pour les sciences de la vie et la santé

BAM: Binary Alignment/Map

BMC: BioMed Central

C^3G: Canadian Centre For Computational Genomics

CAD: Collecteur Analyseur de Données

CADTH: Canadian Agency for Drugs and Technologies in Health

Can: Cancer

CCMG: Canadian College of Medical Geneticists

CCNE: Comité Consultatif National d'Ethique

CDC: Centers for Disease Control and Prevention

CEREES: Comité d'Expertise pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé

CES: Clinical Exome Sequencing

CEST: Commission de l'éthique en science et en technologie

CGES: Clinical Genome and Exome Sequencing

CGP: Centre of Genomics and Policy

CIHR: Canadian Institutes of Health Research

CLIA: Clinical Laboratory Improvement Amendments

CNIL: Commission Nationale Informatique et Libertés

CPP: Comité de Protection des Personnes

CRefIX: Centre de Référence, d'Innovation, d'eXpertise, et de transfert

CSER: Clinical Sequencing Exploratory Research

DGOS: Direction Générale de l'Offre de Soins

DGS: Direction Générale de la Santé

DNA: DeoxyriboNucleic Acid (ADN in French)

DSS: Direction de la Sécurité Sociale

ELSI: ethical, legal, social and policy issues

EMA: the European Medicines Agency

ESHG: European Society of Human Genetics

ExAC: Exome Aggregation Consortium

FDA: the Food and Drug Administration

FMR: Fondation Maladies Rares

FR: France

gnomAD: Genome Aggregation Database

HAS: Haute Autorité de Santé

HC: Health Canada

HGMD: Human Gene Mutation Database

HSO: the Health Standards Organization

HTA: Health Technology Assessment

IBC: International Bioethics Committee

IF: Incidental Finding(s)

INCa: Institut National du Cancer

INDS: Institut National des Données de Santé

INESSS: Institut National d'Excellence en Santé et Services Sociaux

ISO: International Standards Organisation

LDTs: Laboratory-developed tests

MERRI: Missions d'enseignement, de recherche, de référence et d'innovation

MoH: Ministry of Health

MoHSS: Ministry of Health and Social Services

MSSS: Ministère de la Santé et des Services Sociaux

NCBI: National Center for Biotechnology Information

NGS: Next-Generation Sequencing

NSERC: Natural Sciences and Engineering Research Council

OECD: Organisation for Economic Co-operation and Development

OMIM: Online Mendelian Inheritance in Man

OPECST: Office Parlementaire des Choix Scientifiques et Technologiques

PFMG2025: Plan France Médecine Génomique 2025

PI: Principal Investigator or Group Leader

PM: Personalized Medicine

QC: Quebec

QNPHC: Quebec Network of Personalized Health Care

RAMQ: Régime d'Assurance Maladie du Québec

RD: Rare Disease(s)

RNA: RiboNucleic Acid

SFCE : Société Française de lutte contre les Cancers et les leucémies de l'Enfant et l'adolescent

SNDS: Système National des Données de Santé

SSHRC: Social Sciences and Humanities Research Council

UNESCO: United Nations Educational, Scientific and Cultural Organization

VCF: Variant Calling File

VUS: Variants of Unknown Significance

WES: Whole Exome Sequencing

WGS: Whole-Genome Sequencing

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to thank my two supervisors, Yann Joly and Anne Cambon-Thomsen. Yann, thank you for hosting me at the CGP (Centre of Genomics and Policy), for your four years of support, guidance, motivation and intellectual stimulation. Thank you for trusting me to be your first PhD student, and for all the opportunities to collaborate with you and the best Canadian and international leaders in the field of GE^{3}LS. Thank you as well for giving me multiple opportunities to present my results in local and international conferences, and to teach in several human genetics classes. Anne, thank you for taking me on as your last PhD student. You have been a mentor for eight years, and it is an honor to have had the opportunity to work with you throughout these years, on this PhD as well as so many other projects. Thank you for steering me in the right direction in my career as well as my academic endeavours.

Thank you Bartha Maria Knoppers for agreeing to host me in your lab, and allowing me to work with Yann. Thank you as well for your invaluable input throughout the thesis as a member of my supervisory committee, and for forcing me to think not ten, but twenty-five years ahead. It has been a true honor to be a part of your team at the CGP. Thank you Emmanuelle Rial-Sebbag for hosting me at the Allées Jules Guesde lab, for your support and availability during my stays in Toulouse.

I would also like to thank the two other members of my supervisory committee, David Rosenblatt, and Jacek Majewski, for taking the time to hear about my progress throughout the years, and for their guidance and support.

In Toulouse, I would like to give special thanks to Sophie Julia, Anna Pigeon, Alexandra Soulier, Gauthier Chassang, Henri Jautrou, Laurence Mabile, Rosario Sanchez and Nina Segura for making me feel at home when staying in Toulouse, and for their invaluable help in the French part of the thesis.

At the Centre of Genomics and Policy, I would like to give special thanks to Katie Saulnier, Karine Sénécal, Derek So and Forough Noohi, whom with I have collaborated directly, and who have been there along the way to discuss my methods and results, revise my manuscript drafts, prep me for my presentations and support me along the way.

At the department of Human Genetics, I would like to thank Ross McKay and Rimi Joshi. Without their vital help, constant availability, creative thinking and thorough knowledge of the McGill procedures, I would not have been able to overcome all the administrative hurdles this joint PhD represented.

Mathias Rojo, I am so glad this Toulouse-Montreal connection brought us together. Thanks for being the only other geek to respond to my calling to create a co-tutelle support group, and for being such a great friend.

Palmira Granados and Amy Pack, thank you for your unlimited moral support in the happiest and toughest moments of the past four years. You have been my confidents, and the two pillars of my stay at the CGP, and of my life in Montreal. Thanks Amy for being my best sports partner and for always being up for new adventures! Gacias Palmis por compartir lo mejor y lo peor de la vida de inmigrante en Canadá, y por las numerosas y vitales sesiones de soporte en nuestro rincón secreto.

I would also like to thank my friends from Paris, Barcelona, Montreal and around (Chanel Lépinoy Saint-Germain, Justine Callies, Marion Sourdois, Charlotte Izard, Pierre Cannet, Célia Cotinaud, Silvia Speroni, Luis Marin, Gaëtane Boelens, Moshe Mizrahi, Maïte Abad, Sonja Reiland, Michela Bertero, Rahel Park, Manas Gupta, Karelle Lafrenière, Renata Bahous, Jean Monlong, Emma Brasell, Sonia Malek, Sandie Crane, Marie-des-Neiges Magnan, Emma Cobb and so many others). Through skype, WhatsApp, or in person, your support has been vital. Thank you for the long conversations, for your continued friendship even through the distance, for letting me sleep over whenever I visit, and for helping me be who I am!

None of this would have happened without my parents, Marie-Hélène and Eric, and my siblings Jérôme and Alice. Thank you for your unconditional love and continuous support, and for accompanying me daily in this journey. Maman, merci de toujours croire en moi, et de m'avoir toujours encouragée à continuer mon éducation même quand ce n'était pas le choix le plus facile.

Finally, Simon, you are the absolute greatest finding of my PhD. Thank you for opening your heart, and welcoming me in my new family in Montreal.

THESIS PREFACE

This manuscript-based thesis consists of 8 chapters.

Chapter 1 introduces the theoretical framework, topics and concepts relevant to the thesis project. It also describes the overall objectives, hypothesis and research questions.

Chapters 2-6 are original research chapters, containing manuscripts for which the thesis author is the first author. Chapter 2 contains a manuscript that was published in BMC Medical Genomics in 2016[1]. Chapter 3 contains a manuscript that was published in Critical Reviews in Clinical Laboratory Sciences in 2017[2]. Chapter 4 contains a manuscript that was published in Life Sciences, Society and Policy in August 2018[3]. Chapter 5 contains a manuscript that published in the European Journal of Medical Genetics in April 2018[4]. Chapter 6 contains a manuscript currently in preparation. The specific contribution of each author of the manuscripts presented in Chapters 2-6 are detailed in the preface of each Chapter. Chapter 7 contains a discussion of the whole thesis's results. Chapter 8 contains concluding statements.

Appendix A lists other publications to which the thesis author has contributed during the course of the thesis project. Appendix B and C contain supplementary material for Chapters 2 and 4, respectively.

CHAPTER 1: INTRODUCTION

This project's objective is to collect empirical evidence on the clinical implementation of next-generation sequencing technologies in France and Quebec. This evidence, which we collected through a systematic literature review (Chapters 2 and 3), a multiple case-study analysis (Chapters 4 and 5) and a narrative review of the relevant policy landscape (Chapter 6), should be of high interest to health policy makers in both regions. In this introductory chapter, we will therefore define the conceptual framework of evidence-based policy making in personalized and genomic medicine in the context of the French and Quebec healthcare systems.

1.1 From medical practice to healthcare policy: the role of empirical evidence

1.1.1 The role of research in improving healthcare

The practice of medicine is by essence an evolutive art that uses scientific advancements in order to continuously improve the quality and efficiency of care. Indeed, research in biology has enabled the increased understanding of mechanisms underlying the development of diseases associated with morbidity and mortality. This evolving knowledge enables the development of new preventive, diagnostic and curative techniques used in medicine. Medical doctors in most developed countries are therefore required to follow continuous training and education, in order to be able to always offer the best quality of care considering the current available knowledge[5]. At the governmental level, facilitating the integration of research results into medical practice is hence key to achieving sustained health improvements for the population[6]. This integration can take many shapes and forms, including the design of nation-wide prevention campaigns or screening programs, investments in new technologies in order to improve the efficiency, rapidity and accuracy of disease diagnosis, or making new drugs available to patients.

1.1.2 Empirical evidence: the path from patients to citizens.

For an intervention to become "standard of care", or for its' use to be standardized and generalized to all patients who could benefit from it, several paths can be followed. Medical doctors and researchers who conduct research involving human subjects usually disseminate their results in scientific publications, and at professional conferences, which can lead to increased awareness and use in practice. Local healthcare institutions also regularly update their guidelines and standards to reflect emerging scientific consensus and recent advances in medicine. Professional societies also regularly publish position statements, guidelines and recommendations on novel practices. Certification, usually provided by internationally recognized bodies such as the International Standards Organization (ISO), the Health Standards Organization (HSO) in Canada or the Clinical Laboratory Improvement Amendments (CLIA) standards in the USA, is another process through which an institution can validate a new clinical offer, whether it is a laboratory test or the use of new equipment. Technologies are often assessed through standardized processes described as Health Technology Assessment, or HTA[7–9]. Finally, health ministries and governments produce healthcare policies which are applied on a broader scale, ex. at the provincial (Quebec) or national (France) level. Although they may be influenced by political factors, societal preferences or hype, all these processes are ideally based notably on the rigorous collection and analysis of available evidence. The term describing the use of empirical and statistical evidence produced through basic, translational and clinical research in the production of health policies is coined: evidence-based healthcare policy making[10–16]. The collection of empirical and scientific evidence is not the only strategy used in the design of governmental policies. They are also elaborated based on consensus building strategies among all relevant stakeholders, who have their constraints, needs and priorities [13,17–20]. Attention to potential ethical, legal and social issues (ELSI) is also key[21], and more generally policies should be drafted in accordance with broad societal values and goals promoted by governments, such as improving the health of citizens[16,22] .

1.1.3 Evidence-based healthcare policy in universal healthcare systems

In the context of universal healthcare systems, such as those in place in France and Canada, access to required care is provided at little to no charge to all citizens[23] through governmental

budgets. The key for such systems is hence to establish what care is considered "required" or "elective" care. In a context of rising healthcare and innovation costs[24,25], and limited governmental resources, another key challenge in analysing the evidence at hand is to establish new interventions' cost-efficiency. In other words, new interventions will generally be deemed "required" and offered free of charge to all citizens if they strike the right balance between clinical utility and cost-efficiency, especially compared to the standard of care. Multiple stakeholders are involved in establishing such calculations, including healthcare practitioners, health economists, and patient representatives. A new intervention will likely be adopted if it provides increased clinical utility at an equal or lower cost than standard of care. However, an intervention which provides higher benefits at an increased cost will generally need to demonstrate favourable results from a comprehensive cost-benefit analysis in order to be covered by the government. Universal healthcare systems hence invest in research endeavours, continuously collect empirical evidence, and can periodically decide to reimburse new interventions if they provide overall benefits at an acceptable cost.

1.2 From Personalized Medicine to Clinical Genomics

This thesis explores the direct use of NGS technologies in the practice of medicine. I conceive this as being the second era of personalized medicine (PM), also referred to as the era of clinical genomics. In the following sections, I will therefore introduce the concept of personalized medicine, and discuss the first era of PM, in which genomics research results are translated into care, before describing the era of clinical genomics.

1.2.1 Conceptual framework

Personalized medicine (PM), or precision medicine, are concepts which have been popularized and discussed heavily in the academic and non-academic literature since the early 2000[23]. Defining these partly overlapping concepts is a challenge[26], but they have been used as a conceptual framework by a variety of government bodies to generate modern healthcare and health research policies. PM has been portrayed as a way for governments to tackle a number of challenges that health systems face in developed countries: an ageing population, affected by

more and more chronic diseases[25], a costly and inefficient drug development environment, which produces and sells compounds that are inefficient in large patient populations[27], increased inequalities in access to care, and unsustainably rising overall healthcare expenses[28].

In this context, a system which helps providing "the right treatment to the right patient at the right time"[29] through the use of improved patient stratification strategies, holds a promise for reduced costs, increased clinical utility and greater public health benefits. The personalized medicine coalition, a US based advocacy group for PM, defines personalised medicine as "an evolving field in which physicians use diagnostic tests to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records and circumstances, personalized medicine allows doctors and patients to develop targeted treatment and prevention plans" [a],[27].

For some, personalised medicine is broader than that, and encompasses both the use of novel technologies -especially in genomics- to collect data on patients, and a more holistic view of medicine where patients are at the core of intervention, and take a more active role in their own healthcare. It has been described by Guchet as aiming to combine the «molecular-personal » (collection of objective measures analysed through big data informatic algorithms) with the « subjective-personal » (information on individuals' preferences, and socio-cultural background) in the delivery of personalised care[23]. One of broadest definitions or personalized medicine, stemming from the field of systems biology, is that of the 4P medicine: personalized, predictive, preventive and participatory. The added dimension of this definition is the focus on prevention, and the shift from a reactive to a proactive approach of medicine, in which actions are taken before disease symptoms develop, which also contributes to a reduced overall burden of disease[30]. It therefore combines interventions on individual patients, and public health measures such as population screening programs.

The concept of precision medicine, however, is more specific, and has been intimately linked with genetics and genomics from it's inception. This tight connection between precision medicine and genomics is attested notably by a 1997 article which uses the term to describe the revolution that identifying all genes would bring to the practice of medicine and its impact on

[a] http://www.personalizedmedicinecoalition.org/About_Us/About_PMC

human health[31]. This term first made its way into healthcare policy in north America in a 2011 report from the National Research Council of the United States National Academies[23] which defines precision medicine as a way to develop a new taxonomy of disease based on molecular markers[32,33]. The 2015 announcement by President Barak Obama of the launch of the Precision Medicine Initiative[a] dramatically increased the media and the public's interest in the term, which is now used interchangeably with personalised medicine.

1.2.2 The first era of personalized medicine: integrating genomic research results in care.

Although many argue that personalization is at the core of the practice of medicine since the origins, and was already advocated by Hippocrates 400 years Before Christ[28,32,34] and applied in practice by William Osler in the early 1900s[34], the concept has taken a new spur of meaning since the development of DNA (Deoxyribonucleic acid) sequencing technologies. Indeed, these technologies have enabled access to a four-letter code, carrying information with a number of unique features which make it so important to the personalization of healthcare. DNA is unique to an individual, identifying, and partly shared with family members. Alterations in the DNA molecule, which can occur throughout life in both germline (egg and sperm) and somatic cells, have been associated to a number of common and rare diseases which have enabled it's use in several care contexts (prevention, diagnostic, disease classification and treatment)[35].

Rapid improvements in sequencing technologies have occurred since 2010, notably through the extraordinary innovations brought by one company which is now dominating the market in a quasi-monopole manner: Illumina[b]. Next-generation sequencing technologies (NGS) enable the rapid and low-cost transformation of DNA molecules into a digital sequence of A, T, C and Gs. It relies on a series of complex manipulations of the molecule through chemical compounds, an ultra-high-resolution camera, and data processing algorithms which convert image data into a digital letter sequence. Digital files generated by NGS machines are then further processed in three main steps: First, the short digital sequence reads are pre-processed, and low-quality reads discarded. This generates a FastQ file. Second, high quality reads are aligned to a reference

[a] https://allofus.nih.gov/
[b] https://www.illumina.com/

genome, which generates a BAM (Binary Alignment/Map) file. Third, variations from the reference are "called" and generate a variant calling file (VCF) in a table format.

The two technologies which this thesis will mainly focus on are Whole-Genome Sequencing (WGS) and Whole-Exome Sequencing (WES). In WGS, the complete DNA molecule, which contains 3 billion base-pairs, is sequenced, aligned and processed. Variations from the reference genome are usually around 3-4 million per individual. WES contains an additional chemical processing step, in which protein-coding sections of the DNA molecule are extracted, or "captured" before they are sequenced. Though the capture of the coding region of most genes, WES VCFs generally contain roughly 25,000 variants per individual, of which ~50% affect the protein sequence. We will also consider RNA (ribonucleic acid) sequencing, which enables the quantification of gene expression, a technology that is particularly relevant in cancer.

These technologies have been developed and first used in the research context, which has significantly improved our understanding of disease. Indeed, plummeting costs[36], increased technological accuracy and significant progress in data processing strategies have enabled research institutions to sequence thousands of patients and healthy volunteers, which has tremendously improved our capacity to interpret the thousands of variants carried by each individual. The Online Mendelian Inheritance in Man (OMIM), a database focusing mostly on rare diseases, currently lists 6,185 phenotypes of which the molecular basis is known, and 3,890 genes with phenotype-causing mutations[a]. A more recent and carefully curated database, ClinGen, lists 1,372 curated genes with an impact on disease[b], and 950 curated conditions[c]. In what I would call the first era of personalized medicine, these research results have been integrated into healthcare practices and policies in numerous contexts.

The identification of variants that significantly increase a person's risk to develop a disease has been introduced in many population screening programs. Main examples are mutations located in the *BRCA1* and *BRCA2* genes which are associated to breast and ovarian cancer, the discovery of which enabled the development of sophisticated screening programs and preventive procedures[37]. Genomic sequencing has also greatly improved our understanding of rare diseases.

---

[a] http://www.omim.org/statistics/geneMap
[b] https://search.clinicalgenome.org/kb/curations
[c] https://search.clinicalgenome.org/kb/conditions?curated=true

The identification of genes frequently mutated in patients with non-syndromic and complex defects has lead to the development of multiple targeted genetic tests, or gene panels[38]. The sequencing of gene panels, in which one captures from 2 to several hundred relevant genes instead of the whole exome, is sometimes referred to as "targeted NGS" testing. However, in this thesis we will not consider this technology an NGS, since it does not capture information on the whole-genome, and therefore does not pose the same challenges in terms of data storage and interpretation as WES and WGS do. Gene panel sequencing reduces the chance of identifying secondary or incidental findings unrelated to the disease in question, and does not permit regular reanalysis of sequence data in order to find newly identified causal variants.

Numerous variants have been identified which can predict a person's response to pharmacological treatments, enabling the development of pharmacogenomics and companion diagnostic tests[39]. Main successes in this domain have occurred notably in cardiology[40] and oncology[41].

The sequencing of tumor cells from numerous cancer patients has also enabled the identification of numerous disease subtypes, and a more refined classification of cancer patients, which in turn has greatly enriched diagnostic, prognosis and treatment practices. It has also identified molecular commonalities between pathologically different diseases, which can enable drug repurposing or "off-label" use of existing drugs[42–46]. Finally, again especially in oncology, tumor cells sequencing has allowed for the development of personalized therapies, which specifically target a molecular pathway found to drive cancer development[46,47].

Although the use of genetic data in personalized and precision medicine has brought significant hope and are seen positively by most[48], it has also been met by significant criticism. First, the focus on a patient's molecular characteristics can elude other equally important aspects of a patient's experience of the disease, leading to a potentially less humane, more technocratic practice of medicine. Because personalized interventions are sometimes found to be extremely expensive[49], they can be unequally accessible and covered[50,51] , and it can also lower the overall available funding to tackle social determinants of health. Indeed, public health interventions focused on reducing smoking or promoting a healthier lifestyle are key to overall population health[52]. PM also relies heavily on the collection and processing of data from large populations[53], which can challenge the protection of their privacy and expose them to the risk of genetic discrimination[54]. Still, several developed countries have invested heavily in large collaborative

research projects in cancer[a] and rare diseases[b], in large scale population biobanking efforts[c] and implementation endeavours[34] in order to make personalized medicine a reality for patients.

1.2.3 The second era of personalized medicine: using genomic sequencing technologies in the practice of medicine

This thesis explores the emergence of the second era of personalized medicine, in which NGS technologies are used directly in the practice of medicine. This second era of PM can also be referred to as genomic medicine, or "the use of information from genomes and their derivatives (RNA, proteins, and metabolites) to guide medical decision making"[55].

This direct use of NGS in the clinic has been piloted in a number of large academic centers and clinical institutions, since the development of the technology around 2011[56]. It has started with the use of the method in individual patients[57], or families[58] with a particularly challenging condition to diagnose and/or to treat, and is now starting to be used in a more systematic manner in larger populations of patients. We will briefly review the latest evidence in the two most prominent application domains, namely rare diseases and cancer. The use of NGS in public health measures such as pathogen surveillance[59–61], newborn screening[62–68], the sequencing of healthy adults[69–71], or in non-medical contexts such as in direct-to consumer genetic testing[72–75] has also been recently discussed, but will not be explored in detail in the context of this thesis. Although we focused on the use of NGS technologies in both children and adults, the specific issues raised in the pediatric context are explored in Chapter 3.

[a] http://icgc.org/
[b] http://www.irdirc.org/
[c] https://www.geenivaramu.ee/en/access-biobank , https://allofus.nih.gov/about/about-all-us-research-program , https://www.genomicsengland.co.uk/the-100000-genomes-project/ , http://www.genomedenmark.dk/english/vision/

1.3 The current landscape in clinical genomics

1.3.1 Rare diseases

Although individually rare (they are defined as those conditions who affect less than one in 2.000 people in Europe an Canada[a], and less than 200.000 people overall in the US[b]), rare diseases are numerous (more than 7.000 diseases have been identified thus far[c]) and affect a large proportion of the population (3.000.000 Canadians or 30.000.000 Europeans). Most are caused by genetic mutations, have a severe impact on affected individuals' quality of life, and are still untreatable[76]. Significant progress has been made recently thanks to the increased usage of NGS technologies, and open international data sharing, through platforms such as the matchmaker exchange[77].

NGS is used to rapidly uncover the genetic background of a patient's condition, when their phenotypic features are hard to diagnose with targeted testing, or their disease is hard to characterise. Because it tests most genes at once, it avoids the repetitive use of several targeted tests which may come back inconclusive. It can therefore end the "diagnosis odyssey" of patients who have gone through multiple genetic and non-genetic tests, sometimes over the course of numerous years, and still remain without a diagnosis for their condition[78–81].

The efficiency of WES is commonly measured as the diagnosis yield, or the percentage of patients in which causal mutation(s) have been identified and enabled a molecular diagnosis. The reported diagnostic yield of WES is quite variable, as it heavily depends on the type and diversity of conditions targeted, sample size, how stringent patient selection criteria was, and if only probands were sequenced, as opposed to trios (proband + parents), which is an efficient way to uncover *de novo* mutations. Studies published in the last three years have reported diagnosis yields rates of 25 to 60%. (see **Table 1.1** below). The rate is generally higher in pediatric patients compared to adults[82], and higher in consanguineous families[83], and can be higher in trio-based analysis[84]. Re-analysis of sequence data allows to increase diagnostic yield[85,86]. These studies generally report that WES is found to have increased clinical utility as compared to other

[a] https://www.rarediseasefoundation.org/about
[b] https://blogs.cdc.gov/genomics/2016/02/17/rare-diseases/
[c] https://www.rarediseasefoundation.org/about

conventional or targeted tests, although there are exceptions[87]. However, these superior results with WES may be due to a bias of ascertainment, since authors are early-adopters who have invested significant time an effort in setting the stage for clinical implementation of the technology. Another indicator of efficiency of WES is its cost-effectiveness as compared to targeted tests. A recently published systematic review found that reported costs were extremely variable, and that there was no strong evidence that they are dropping, which is often used as an argument to justify the technologies' clinical implementation[88]. A limited number of tertiary care centers in the United States[a], in Canada[b] or in the Netherlands[c] have already implemented WES in routine care for certain patient populations. It is to be noted that the analysis of WES data usually primarily focuses on a limited number of most relevant genes, through a VCF filtering process called "virtual panel" analysis. For instance, Genome Diagnostics Nijmegen offers WES for 27 groups of phenotypes, from heart disorders to epilepsy, skin or vision disorders. For each clinical category, they publish a list of genes they will focus on in the virtual panel, which include from 15 genes for Dyskeratosis congenita, to 3025 genes for Multiple congenital anomalies[d].

1) Table 1.1 Recent examples, use of WES in rare diseases diagnostic

Reference	Patient population	Diagnostic yield
(Chérot et al. 2018) [77]	216 patients, neurodevelopmental disorders	25.9% (56/2016)
(Lazaridis et al. 2016)[79]	51 diagnosis odyssey patients, all conditions	29% (15/51)
(Monroe et al. 2016)[89]	17 patients, intellectual disability	29.4% (5/17)
(Trujillano et al. 2017)[90]	1000 families, 2819 samples sequenced, all conditions	30.7% (307/1000)
(Thevenon et al. 2016)[81]	43 unrelated individuals with undiagnosed intellectual disability and epileptic encephalopathy	32.5% (14/43)
(Thuriot et al. 2018)[91]	51 patients, dysmorphisms of undetermined etiology	35% (18/51)
(Córdoba et al. 2018)[80]	40 patients suspected of having a	40% (16/40)

[a] The Mayo Clinic, University of California Los Angeles Clinical Genomics Center, and Baylor College of Medicine Medical Genetics Laboratories.
[b] Sickids hospital
[c] Genome Diagnostics Nijmegen
[d] http://www.genomediagnosticsnijmegen.nl/index.php/en/services/exome-sequencing-diagnostics

	neurogenetic condition	
(Gauthier-Vasserot et al. 2017)[92]	10 unrelated patients with congenital neutropenia and intellectual disability.	40% (4/10)
(Srivastava et al. 2014)[93]	78 patients, neurodevelopmental disabilities	41% (32/78)
(Bourchany et al. 2017)[94]	29 patients, severe undiagnosed disorders with developmental abnormalities	45% (13/29)
(Alfares et al. 2017)[83]	454 patients from consanguineous unions	49% (222/454)
(Long et al. 2017)[95]	21 children with dilated cardiomyopathy	50% (10/21)
(Cohen et al. 2017)[96]	39 patients, suspected genetic disease	51.3% 20/39
(Tan et al. 2017)[97]	44 children suspected of having a monogenic disorder	52% (23/44)
(Stark et al. 2016)[98]	80 infants with suspected monogenic disease	57.5% (46/80)
(Yavarna et al. 2015) [99]	149 probands from Qatar with suspected Mendelian, mainly neurocognitive phenotypes	60% (89/149)
TOTAL	**2322 patients**	**38.3% (890/2322)**

1.3.2 Cancer

Cancer is a leading cause of mortality and morbidity worldwide[a]. The 5 years survival rate is extremely variable depending on cancer types, age at diagnosis, gender and ethnicity[100]. It can range from 8% in pancreatic cancer, to over 90% in breast cancer[b]. To date, the majority of cancer patients are diagnosed through an analysis of their tumor cells under a microscope, which allows pathologist to establish the stage of their cancer, and serves as the basis to establish a treatment protocol[46]. Few patients who are eligible to receive drugs which have a pharmacogenomic biomarker, have their tumor analysed further with targeted molecular tests. However, several large clinical research programs have been launched in developed countries to establish the clinical utility of NGS in oncology, both in adult and in pediatric patients[101].

The availability of NGS technologies has enabled the molecular characterization of a vast array of cancer types, which has the potential to significantly impact patient care[102]. Indeed, sequencing cancerous cells can provide various type of information potentially relevant for clinical management. Establishing cancer cells mutational profiles enables refined classification and diagnostic[46,103,104]. The presence or absence of certain mutations can predict the likelihood of

[a] http://www.who.int/mediacentre/factsheets/fs297/en/

[b] https://seer.cancer.gov/ , SEER Survival Statistics, all cancer types, 5 years survival interval.

the patient's response to certain available drugs[45]. It can also inform on mutations driving carcinogenesis, which can be targeted by personalized treatments (existing or to be developed through clinical trials) in order to selectively destroy cancerous cells. Finally, as cancerous cells grow abnormally quickly, their mutational patterns evolve rapidly. Disease monitoring can therefore also be done through tumor sequencing.[105] Because tumor cells harbor so many mutations of various types, WES or WGS can be complemented with RNA sequencing, or methylation arrays in order to gain information on gene expression. In a recent review, Leonhard Müllauer summarized the impact of NGS in oncology: "NGS supports diagnosis, identifies therapeutic targets, reveals resistance mechanisms and facilitates disease monitoring. It takes a central function in the implementation of cancer therapies adapted to the molecular alterations of tumours"[105]. Success of genome-wide sequencing in oncology is often measured by the proportion of patients in which causal (driver), and/or targetable (actionable) mutations are identified, however this measure has been criticized as it is not linked with patients outcome[106]. The long-term hope is that these technologies improve patient survival and outcome, and reduce the burden of cancer and the impact of adverse reactions to treatments. It is important to note that cancers occurring in children are very different from that which occur in adults in that they are less likely to be caused by molecular pathways that are influenced by age, or lifestyle (smoking, chemical exposure, etc.…), like some of the more adult cancers. A number of recent clinical trials have been launched to determine the added value of NGS in pediatric cancers[42,43,107–110]. Although they have enabled the identification of actionable variants in 30 to 60% of patients, they have had only mitigated results on overall survival and morbidity, with only a handful of patients in each trial actually receiving matched treatment[111]. Similar results have been obtained in adult patients with advanced cancer[112–114]. Numerous challenges remain in NGS in oncology, including cost and availability of targeted treatment, as well as turnaround time, which is a strong limitation in critically-ill patients[115].

1.4 Empirical evidence needed in France and Quebec: is the time ripe for clinical genomics?

1.4.1 Health systems in France and Quebec

In this thesis, we will examine the policy implications of implementing NGS in the clinic in two specific jurisdictions: France and Quebec. Both jurisdictions share a language (French), a history, and a civil law system, although Quebec follows a civil law system within bijural legal framework of Canada. Both are also partly submitted to a higher regulatory authority, but which has very limited bearing on the specific organization of the healthcare system itself: the European Union for France, and the Federal Government of Canada for Quebec.

Both share the same value of universal access to high quality care for all citizens, however the respective systems bare significant differences. First, while Quebec has a population of 8 million spread in an immense territory of 1.5 million Km^2, France has a population of nearly 69 million in a territory twice as small. The population density is therefore 20 times as high in France as it is in Quebec. This has a significant impact on the structure and delivery of care in the two jurisdictions. It is heavily decentralized in France, with numerous large urban delivery poles, and important roles played by regional institutions, whereas in Quebec it is concentrated around the two main urban regions of Montreal and Quebec City.

Healthcare in Canada is overseen by the Canada Health Act, which describes the primary objective of Canadian health care policy, which is "to protect, promote and restore the physical and mental well-being of residents of Canada and to facilitate reasonable access to health services without financial or other barriers."[a]. The Act establishes the criteria that provincial care delivery programs have to respect in order to benefit from a federal cash contribution; which is around a fourth of total provincial spending [116]. Provincial health insurance plans have to be “publicly administered, comprehensive in coverage, universal, portable across provinces, and accessible”[b]. It is important to note that medical devices and pharmaceutical products are regulated both at the provincial and at the federal level. Both France and Canada spend heavily

[a] Canada Health Act, R.S.C., 1985, c. C-6, article 3
[b] Ibid., article 7

on healthcare, and do so primarily through public funds. Indeed, according to World Bank data from 2014[a], healthcare spending represented 10.4% of GDP in Canada in 2014, against 11.5% of GDP in France, with 70.9% coming from public sources in Canada and 78.2% in France.

In Quebec, the universal health insurance program is administered by the ministry of health and social services through the Quebec medical insurance regime, RAMQ (Régime d'Assurance Maladie du Quebec). Quebec also has its own HTA agency, namely INESSS (Institut National d'Excellence en Santé et Services Sociaux), which is in charge of validating the introduction of novel technologies into the list of publicly funded services. The health system delivery in France combines various regimes of health insurance, including two main ones: the general regime covering all employees and independent workers, and the agricultural regime covering all workers in this sector. Multiple special regimes exist such as the one covering university students. Most residents are covered, on top of the public regime, by complementary private insurance or "mutuelle". Private for-profit and public providers and institutions co-exist, and patients always have the choice of where they receive care, and which provider they go to[117,118]. The main HTA agency is the High Health Authority (Haute Autorité de Santé) [119,120] but other national agencies such as the Biomedical Agency (Agence de la Biomédecine) play an important role in ensuring high quality standards coordinating care delivery throughout the territory.

1.4.2 The need for new empirical evidence in clinical genomics

Both France and Quebec/Canada have invested significant resources in genomics research, notably through the creation of large sequencing centers with significant data production, storage and analysis capacity: The McGill University and Genome Quebec Innovation Center[b], and the National Genotyping Center in France[c]. Numerous researchers in France and Quebec teams are active in research, and publish their genomics research results regularly[43,81,121–128]. However, at the start of this project, neither governments had officially embarked in publicly funded clinical genomics endeavours. In April 2016 however, France announced the launch of a 9 years national medical genomics plan to organise access to NGS technologies throughout the territory[129]. This

[a] World bank data, https://data.worldbank.org/
[b] http://www.mcgillgenomecentre.org/
[c] https://www.cng.fr/index.html

highlights one of the main challenges we faced in this project, which was to cope with the fast and continuous evolution of both NGS techniques and clinical genomics policies, which were published and updated regularly throughout the duration of the project.

We decided to tackle our objective, which was to contribute to the body of evidence available to policy makers on the clinical implementation of NGS, with an original approach, using quantitative and qualitative analysis methodologies in social sciences to study this highly technical, fast-evolving topic. Following strategies drawn from implementation science [34], we designed our project in order to have access to both international data (through a review of the available literature), local evidence from the field (through a multiple case-study analysis) and to critically analyse the policy landscape. This approach is meant to allow us to provide a basis for the design of highly efficient clinical genomics policies in France and Quebec.[130]

1.5 Objective, hypothesis and research questions

Our objective was to contribute to the body of evidence available to policy makers on the clinical implementation of NGS. More specifically, we aimed to assess if a responsible and efficient use of NGS in clinical care could be impeded by policy gaps in France and Quebec.

Currently, the clinical interpretation of a patient's genome sequence data is done through the intervention of many stakeholders including basic science researchers. These researchers use bioinformatics tools, processes and norms developed for research to filter and analyse patients' NGS data. In parallel, existing regulatory frameworks have been developed for the use of genetic data, with no specific provision on genomic information. We hypothesised that this creates a strong need for standardization of practices, and may require changes in current regulatory frameworks. Policy gaps may still be present after the publication of genomic medicine plans in France and Quebec.

With this objective and hypothesis in mind, we aimed to answer the three following research questions:

(1) What issues do technology users experience and foresee when using NGS data to inform patient care? (Chapters 2 and 3)

(2) How are patients' NGS data currently managed (produced, accessed, analysed, and shared) in clinical institutions in Quebec and in France? (Chapters 4 and 5)

(3) Are there gaps in the current regulatory frameworks which should be addressed to enable a responsible and efficient standardized use of NGS in the clinic? (Chapter 6).

CHAPTER 2: GENERAL SYSTEMATIC REVIEW OF THE LITERATURE

Preface

In this chapter, we aimed to address our first research question: What issues do technology users experience and foresee when using NGS data to inform patient care?

The choice to focus on technology users was twofold: first, when we designed our study, several publications were already addressing the opinions and experiences of patients, families[131–133] and clinicians[133–137], or discussed issues with clinical genomics from an ethical, legal or social point of view[138–143]. Second, we were interested in identifying implementation issues which were directly reported by professionals using the technology in the context of care. The decision to focus on whole-exome sequencing, and not mention specifically whole-genome sequencing in our search terms stemmed from discussions with genomics researchers and clinical geneticists, and an initial scoping review of the literature. From this preliminary look at the field, it appeared that WGS was still mostly used in the context of research, whereas WES was starting to be used as a basis for clinical decisions. In addition, our search did identify a number of articles discussing both technologies, and many of the issues we uncovered about WES are also relevant for WGS. The systematic literature review methodology was the most appropriate first step in identifying all potential unsolved issues reported to date, with no geographical or clinical domain restriction. The main limitation of this method is that it provides a fixed snapshot of the available evidence, which stops at the date at which the search is conducted. Considering the pace at which studies are published, and the rapid technological progress in NGS, it is possible that a search conducted three years later would yield significantly different results.

Specific authors' contributions (as published in the manuscript):

- Gabrielle Bertier conceived the study, designed the search strategy, performed the search and collected all the data, filtered and coded the articles, performed the analysis and wrote the first version of the manuscript.

- Martin Hétu filtered and coded the articles, and commented on the manuscript.
- Yann Joly provided guidance on the design of the study, methodology and analysis. He commented on the manuscript.
- All authors read and approved the final manuscript.

The manuscript was published in BMC Medical Genomics in 2016, and is accessible in open access at the following link:
https://bmcmedgenomics.biomedcentral.com/articles/10.1186/s12920-016-0213-6

UNSOLVED CHALLENGES OF CLINICAL WHOLE-EXOME SEQUENCING: A SYSTEMATIC LITERATURE REVIEW OF END-USERS' VIEWS.

Gabrielle Bertier[1,2*], Martin Hétu[1], Yann Joly[1]

1. Centre of Genomics and Policy, McGill University.
2. Université Toulouse III Paul Sabatier and Inserm UMR 1027

* Corresponding author

Gabrielle Bertier, gabrielle.bertier@mail.mcgill.ca
Centre of Genomics and Policy | McGill University
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1, Canada
-
UMR 1027, Inserm, Univ Toulouse III - Paul Sabatier
37 allées Jules Guesde F-31000 Toulouse, France

Martin Hétu, martin.hetu@mail.mcgill.ca
Centre of Genomics and Policy | McGill University
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1, Canada

Yann Joly, yann.joly@mcgill.ca
Centre of Genomics and Policy | McGill University
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1, Canada

2.1 Abstract

Background: Whole-exome sequencing (WES) consists in the capture, sequencing and analysis of all exons in the human genome. Originally developed in the research context, this technology is now increasingly used clinically to inform patient care. The implementation of this technology into healthcare poses significant, organizational, regulatory, and ethical hurdles, which are widely discussed in the literature.

Methods: In order to inform future policy decisions on the integration of WES into standard clinical practice, we performed a systematic literature review to identify the most important challenges directly reported by technology users.

Results: Out of 2094 articles, we selected and analyzed 147 which reported a total of 23 different challenges linked to the production, analysis, reporting and sharing of patients' WES data. Interpretation of variants of unknown significance, incidental findings, and the cost and reimbursement of WES-based tests were the most reported challenges across all articles.

Conclusions: WES is already used in the clinical setting, and may soon be considered the standard of care for specific medical conditions. Yet, technology users are calling for certain standards and guidelines to be published before this technology replaces more focused approaches such as gene panels sequencing. In addition, a number of infrastructural adjustments will have to be made for clinics to store, process and analyse the amounts of data produced by WES.

2.2 Background

Whole-exome sequencing (WES) consists in the capture, sequencing and analysis of all exons of all protein coding genes in the human genome. Instead of analyzing the whole genome, composed of roughly 3 billion base-pairs, WES focuses only on the approximately 30 million base-pairs which are translated into functional proteins, in which mutations are the most likely to have a severe direct phenotypic consequence. WES can therefore be considered a much less costly and more efficient method of identifying all possible mutations in genes compared to other methods such as genome-wide association studies or whole-genome sequencing (WGS)[144]. WES was originally used mainly to identify rare mutations contributing to Mendelian diseases, as compared with the many variants involved in common complex diseases[55], although this distinction can be considered artificial[145]. Methodologies evolve rapidly, and new software enable this technology to better detect complex genetic changes such as structural variants[146] and copy-number variants[147–149]. The integration of WES into healthcare is already underway, contributing to the development of personalised medicine[55]. It is currently used clinically for numerous purposes, ranging from diagnosis to disease prognosis and treatment decisions[150]. Analysing a patient's exome through one test is now less costly than testing a number of specific genes, especially when little is known about the genetic background of the disease, although this analysis does "add layers of complexity to test interpretation"[151]. In addition to the technical

challenges of making the technology fit for clinical diagnostics (improving exon capture, sequencing coverage, read length, accurate detection of insertion-deletions, and reduction of false positive and false negative rates), numerous hurdles have to be overcome to use WES in routine healthcare. A number of ethical, legal, social and policy (ELSI) challenges have been extensively discussed in the literature by scientific researchers as well as policymakers and professional societies [152–157]. Guidelines have been produced to respond to some of these challenges, notably that of reporting incidental findings (IF). The American College of Medical Genetics and Genomics (ACMG) published a policy recommendation on this topic in 2013 [158], which has been heavily discussed [159–162], and updated in 2014 [163]. The European Society of Human Genetics, in turn, published a recommendation in 2015 [164]. The Canadian College of Medical Geneticists published a position statement in 2015 to frame the "clinical application of genome-wide sequencing for monogenic diseases in Canada" [165]. But in order to design efficient policies aimed at enabling the responsible integration of WES into healthcare, there is the need to systematically identify what the prominent challenges are. To our knowledge no study has yet been published on the implementation hurdles identified directly by scientific researchers and medical doctors (technology users) reporting on the clinical use of WES. With this objective in mind, we designed a systematic review of the literature to identify the most important challenges directly reported by technology users.

2.3 Methods

Our systematic literature review methodology was adapted from the PRISMA guidelines [166] and the Petticrew and Roberts practical guide [167].

2.3.1 Studies sources

6 databases were searched to identify the most comprehensive list of publications. The last search was performed on March 31st, 2015.

1. EBSCO host digital archives http://www.ebscohost.com/archives
2. Embase http://www.elsevier.com/online-tools/embase/
3. NCBI Pubmed http://www.ncbi.nlm.nih.gov/pubmed/

4. Science Direct http://www.sciencedirect.com/
5. Scopus http://www.scopus.com/
6. Web of Science http://apps.webofknowledge.com/

2.3.2 Choice of keywords

Since our objective was to identify reports published by technology users on the clinical use of WES, we used the following keywords in combination to stringently filter out reports from outside the clinical context: Clinical application, Medical application, Healthcare, Clinical care, Medical care, Clinical practice, Clinical diagnostic, Medical practice.

Therefore, the complete search used was the following: ("exome sequencing" OR "whole-exome sequencing" OR "whole exome sequencing") AND ("clinical application" OR "medical application" OR "healthcare" OR "clinical care" OR "medical care" OR "clinical practice" OR "clinical diagnostic" OR "medical practice")

2.3.3 Screening, filtering and selection

We searched for the chosen keywords using the full text of articles and reports without any date or language restrictions. The search resulted in 2275 articles (details available in **Table 2.1: Total number of hits by database**). All results were then aggregated in a single Excel file, from which we removed duplicates, resulting in 2094 unique articles.

2) Table 2.1: Total number of hits by database

Database searched	Total hits
EBSCO academic search complete	893
EMBASE	258
NCBI Pubmed	123
Science Direct	722
Scopus	160
Web of Science	119
TOTAL	2275
Total unique articles	2094

Further screening for articles to filter out was done in three steps:

- First, we screened out results that were not peer reviewed journal articles (such as abstracts from conference oral presentations or posters, blog articles, or conference programs).
- We then removed articles that were not written in English, French or Spanish.

At this point, both GB and MH processed with filtering the articles in parallel. We filtered the articles according to the following inclusion and exclusion criteria:

- The articles are written by a technology user, defined as a medical doctor, life science researcher or medical researcher who is directly exposed to the technology in his field of expertise. At this point we excluded articles for which the corresponding author was a researcher in policy or human and social sciences.
- The articles directly address WES. At this point we excluded articles which, for instance, simply referred to other studies which had used WES. We included articles that talked about other technologies in addition to WES, such as WGS or gene panels.
- The articles discuss the clinical implementation of WES. At this point we excluded articles which only considered WES in the context of basic research or discovery.
- The articles list unsolved implementation challenges. We excluded articles which did not mention any challenge linked to the clinical implementation of WES, which listed challenges already solved, or which described them as easy to solve through measures already partly in place. We also excluded articles which we tagged as 'recommendations' when they consisted of a list of solutions for the clinical implementation of WES and did not describe any challenge or issue as 'unsolved'.

After filtering all articles separately, GB and MH compared their selected articles list, discussed any articles selected only by one of them, and agreed on a final decision for each of those articles. Only 10% of articles required discussion (182 out of 1792 articles).

The full list of selected articles is available in supplementary material. The results of all screening and filtering steps are described in **Table 2.2: Screening and filtering process**.

3) Table 2.2: Screening and filtering process

	Total	Removed
Total Articles	2275	
Screening		
Removing duplicates	2094	181
Peer reviewed journal articles	1810	284
Written in English, French or Spanish	1805	5
Accessible	1792	13
Filtering		
Included	147	1645

2.3.4 Coding

Since our objective was to be as comprehensive and unbiased as possible in the identification of unsolved challenges relevant to technology users, the coding of articles was done through inductive content analysis[168,169]. An initial list of challenges was generated by GB on the basis of an analysis of 30 articles selected at random (20% of all selected articles). These challenges were then discussed and adjusted by all co-authors together. Some similar challenges were merged, while others were split into separate challenges. Additional challenges were added both by MH and GB over the course of the analysis if five articles or more were found to refer to any specific challenge. For the data analysis, we decided to group challenges along a typical 'timeline' ranging from data production, to analysis, reporting and finally sharing.

2.4 Results

2.4.1 Studies scope

2.4.1.1 Publication dates

The first articles selected were published in 2010, which is consistent with the appearance of WES technology in the scientific literature. 3 articles (2%) were published in 2010, 13 (9%) in 2011, 31 (21%) in 2012, 42 (29%) in 2013, 46 (31%) in 2014 and 12 (8%) in the first trimester of 2015, when we performed the search.

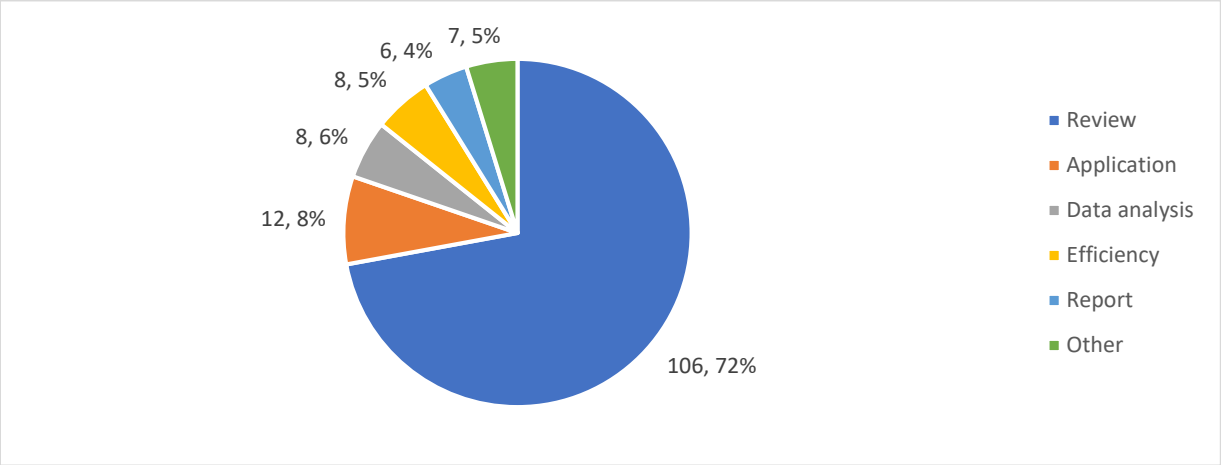
2.1.1.2 Whole-Exome Sequencing/Next-Generation Sequencing/High-Throughput Sequencing

Among the selected articles, only 48 (34%) focused exclusively on WES. The other 94 articles either discussed challenges linked to other technologies such as WGS or large gene panels, or discussed challenges linked to Next-Generation Sequencing or High Throughput Sequencing (including WES and other technologies) in general.

2.4.1.3 Article types

A graph representing all article types is available in **Figure 2.1: Selected articles types**. Of the selected 147 articles, the vast majority (106, 72%) are review articles in which the authors do not report directly on the way they personally use WES, but rather review the current body of evidence about a certain aspect of the technology. The majority of review articles (66, 62% of reviews) describe the impact of WES on a specific disease or disease group, and 5 (5% of reviews) generally discuss its use in the diagnosis of various diseases, whereas 25 (23% of reviews) review the technology in general, including both its research and clinical applications. 6 articles (6% of reviews) describe how the technology may impact a specific medical field, such as nursing[170] or pathology[171] while 4 (4% of reviews) focus on pharmacogenomic applications. 12 articles (8,2%) report directly on applications of the technology for a specific patient[56,172], a family[173], a selected group of patients [174–176], or on a larger scale for a particular healthcare service[177–182]. 8 articles (5.4%) discuss the efficiency of WES compared to other techniques, such as gene panels or WGS. 6 articles (4%) report on the use of a technology other than WES, and explain this choice by identifying challenges with WES. Finally, 8 articles (5,4%) focus on challenges linked with WES data processing, analysis and interpretation.

1) Figure 2.1: Selected articles types



Legend:

- Review: the authors do not report directly on the way they personally use WES, but rather review the current body of evidence about a certain aspect of the technology
- Application: authors report on the application of WES on a specific patient, family, or a larger group of patients in a healthcare service.
- Data analysis: authors focus on challenges linked with WES data processing, analysis and interpretation.
- Efficiency: authors compare the efficiency of WES compared to other techniques, such as gene or gene panels sequencing.
- Report: authors report on the use of a technology other than WES, and explain this choice by identifying challenges with WES

2.4.1.4 Disease focus

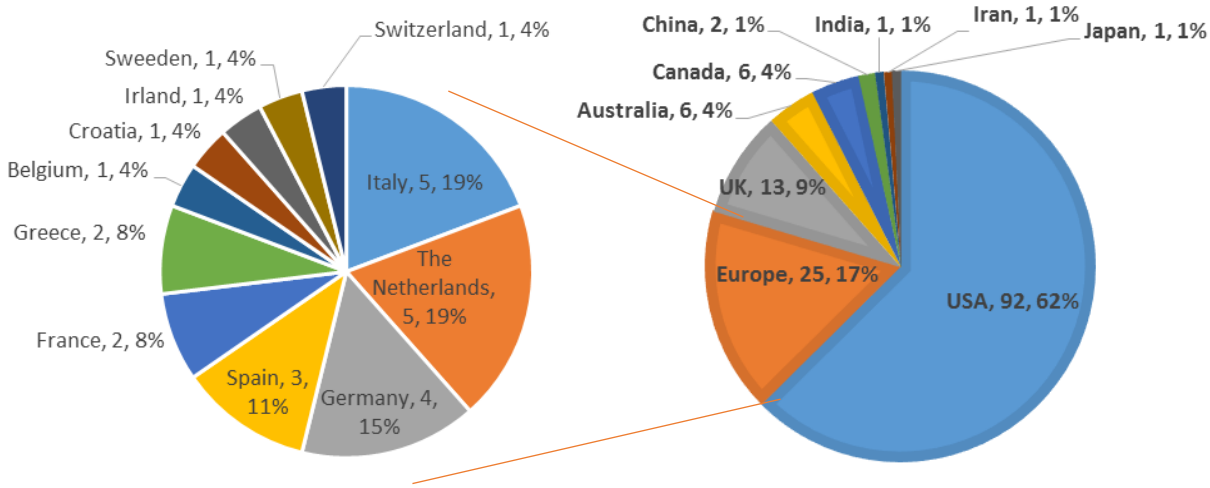
Our first observation was that the articles selected cover an extremely wide range of diseases, from cancer (26, 29%) to rare diseases (24, 16.3%) to common disorders such as intellectual disability and developmental delay (6, 4%). 14 (9.5%) articles focus on a diversity of heart diseases, 13 (14%) on neurological diseases, and 3 (2%) respectively on blood, muscle, and kidney disorders. It is a particularly challenging task to group the diseases addressed by our selection of articles in relevant categories for three main reasons. Firstly, those categories may partly overlap: for instance, cancer in children is considered to be a rare disease. Secondly, a

number of articles (9, 6%) focus generally on genetic or inherited disorders, which may or may not be rare diseases. Thirdly, some articles cover many possible diseases – such as cancer[183,184] or rare diseases[185,186] in general - while others focus specifically on one disease[187–189]. A significant number of articles (42, 29%) did not focus on any diseases, but addressed the impact of WES on all clinical contexts.

2.4.1.5 Country

We noted the country of the institution of corresponding authors of all selected articles. A total of 19 countries were represented. The majority of articles (92, 62%) we selected were written in the USA. 25 (17%) were written in Continental Europe (excluding the UK, which represented an additional 13 articles). The complete distribution of articles per country is represented in **Figure 2.2: Number of articles per country of institution of corresponding author.**

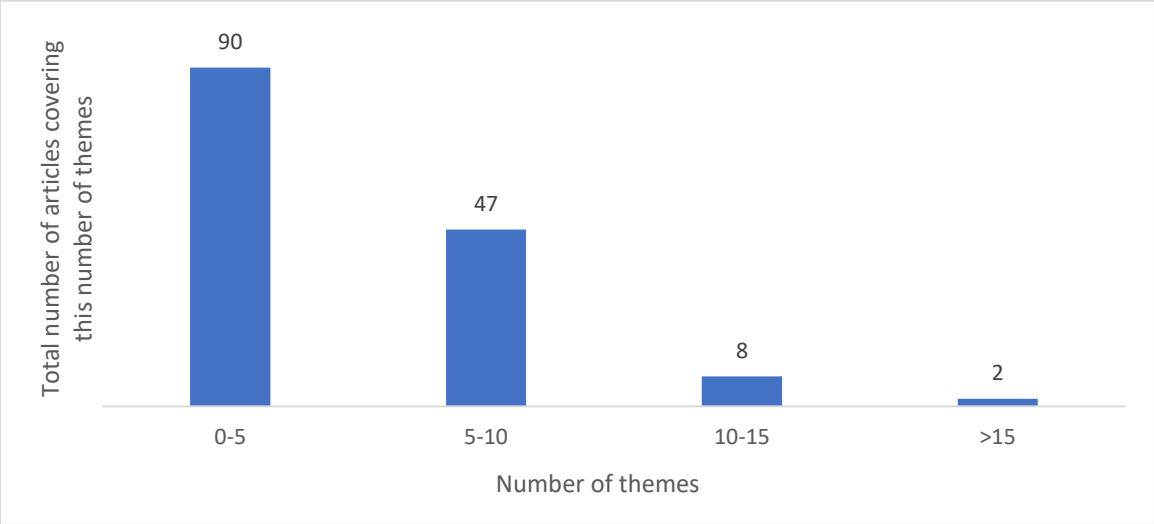
2) Figure 2.2: Number of articles per country of institution of corresponding author



2.4.1.5 Number of challenges treated

On average, the 174 selected articles covered 8 of the identified challenges. The majority of articles (90, 61.2%) covered from 1 to 5 challenges. 47 articles (32%) covered between 6 and 10 challenges, and only 10 articles (6.8%) covered more than 10 challenges. This steadily decreasing distribution shows the importance of the systematic review methodology in identifying all challenges linked to the clinical implementation of WES as identified by technology users. This distribution is displayed in **Figure 2.3: Number of challenges covered across articles.**

3) Figure 2.3: Number of themes covered across articles



2.4.2 Unsolved challenges identified

From the original 147 studies, we identified 23 unsolved challenges. These were divided into 4 categories, following the 'samples and data trajectory', of production, analysis, reporting and sharing.

Table 2.3 briefly describes the challenges found in all articles. **Figure 2.4. List of unsolved challenges and proportion of articles reporting on them** displays the total number of articles covering each challenge. The unsolved challenges reported by technology users are extremely diverse, ranging from very specific challenges, such as the inclusion of WES results in patients' electronic health records, to much broader ones, such as the challenges of communicating results with patients and their families and managing their expectations. Three challenges (henceforth referred to as major challenges) were reported by more than 70 (47,6%) articles:

- the interpretation of variants and variants of unknown significance (VUS) was reported by 92 (62.6%) articles
- challenges linked to incidental findings were reported by 79 (53.7%) articles
- the cost of WES and reimbursement of the test by the healthcare system was reported by 72 (49%) articles.

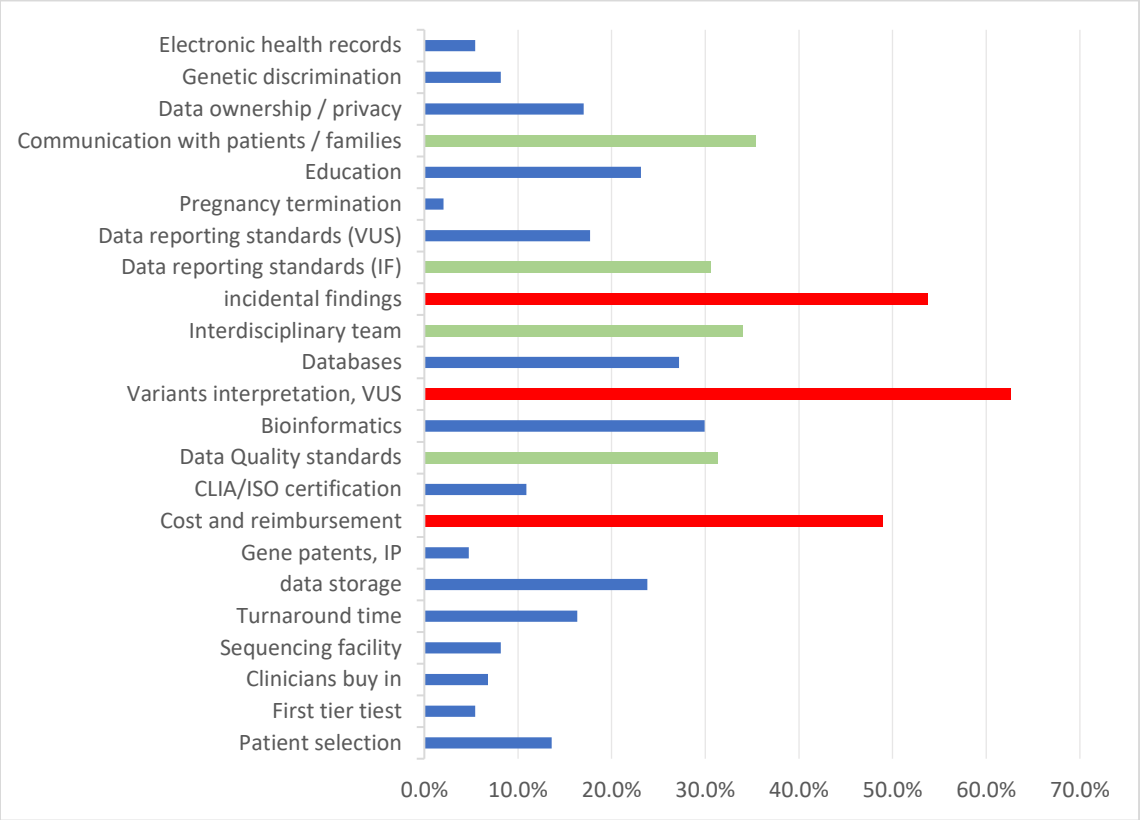
The following sections provide an overview of the terms in which these three challenges are described in the selected articles.

4) Table 2.3: Description of challenges identified

Category	Challenge	Description
Data production	Patient selection	It is difficult to determine which patients would receive a clear clinical advantage from WES.
	First tier test	It may not be clear whether WES should be used as a first tier test, or as a second tier test after the failure of more selective genetic testing such as gene(s) or gene panel(s) testing.
	Clinicians buy-in	Some clinicians are not willing to order WES testing, sometimes because of lack of trust in the technique. This can be an important barrier to clinical implementation of WES.
	Sequencing facility	Decisions will have to be made about whether sequencing should be done in each laboratory offering the test, or if laboratories should order it from centralized sequencing facilities.
	Turnaround time	WES results can sometimes take longer to obtain than more targeted tests, which may challenge their implementation in a clinically relevant timeframe.
	Data storage	WES data requires a large and secure storage space, which may not always be available in a clinical setting.
	Gene patents	In some jurisdictions, patents on the sequence of specific genes may make it difficult to sequence whole exomes without having to pay IP rights.
	Cost and reimbursement	The cost of WES sequencing and analysis may be too high for some clinical applications. Reimbursement strategies for such tests are yet to be established by private insurers and by the healthcare systems.
	CLIA/ISO certification	WES has yet to be standardized in order to obtain CLIA and ISO certification, in the USA and in Europe respectively. This certification is key for clinical implementation and reimbursement of WES by the healthcare systems.
	Data quality standards	There is still no formal agreement on the appropriate quality standards to apply to the technology so that it can be implemented in the clinic.
Data analysis	Bioinformatics	Analysis of WES results relies on a number of bioinformatics tools that have yet to be perfected.
	Variant interpretation, VUS	WES generates a high number of variants per individual, a large proportion of which are still of unknown significance. The extreme difficulty of interpreting these variants has created a bottleneck in the clinical application of the technology.
	Databases	To better interpret variants, WES and more generally NGS results need to be broadly shared. More complete and reliable reference databases linking variants to patients' phenotypes need to be developed.
	Interdisciplinary team	The interpretation of variants relies on the collaboration of different professionals, including medical doctors, bioinformaticians, biologists and clinical geneticists. Integration of WES into the clinic may require that we reconsider the definition of new and

		established professional roles in clinical hospitals.
	incidental findings	WES has the potential to generate a high number of incidental findings. These may create anxiety in patients and the need for costly follow-up procedures if reported.
Reporting	Data reporting standards (IF)	There is a pressing need to develop standards on which a large part of the community can agree regarding whether and how to report IFs to patients and their families.
	Data reporting standards (VUS)	There is a pressing need to develop consensus standards on when and how to report VUS to patients and their families.
	Pregnancy termination	WES may enable the detection of mutations at a time when pregnancy termination is still possible, which was not possible with prior technologies. This leads to the necessity to develop new policy decisions which take into account the ethical justifications behind offering pregnancy termination options for these conditions.
	Education	Increased use of WES in the clinic will mean that a growing number of healthcare professionals will need to interpret these data, and therefore need to be educated in the basics of genetics and genomics. This is not the case today, as very few medical staff currently have genomics knowledge.
	Communication with patients and families	The amount and complexity of the data produced by WES complicates the task of healthcare professionals who have to report WES results to patients. In specific circumstances, they may also have a duty towards some of their patients' family members. Many more types of results will have to be explained, in longer and therefore more costly pre and post-test counselling sessions.
Sharing	Data ownership / privacy	Given that WES data is inherently identifying and provides some information on the present and future health status of the proband and their families, several privacy and ownership questions have to be resolved: Who owns WES data? How should the access and sharing of this data be regulated?
	Genetic discrimination	The possibility for insurers or insurance companies to access WES data may lead to greater discrimination against potential clients or employees based on their genetic background.
	Electronic health records	The correct interpretation of WES data often relies on accessing a complete description of patients' phenotypic characteristics, which would be greatly facilitated by consulting electronic health records. However, before this can be done public health systems and hospitals will have to decide whether WES results should be added to patients' electronic health records.

4) Figure 2.4: List of unsolved challenges and proportion of articles reporting on them.



Legend: We highlighted the issues found in more than 40% articles (58 total) in red, and issues found in 30 to 40% articles (44 to 58) in green.

2.4.2.1 Data analysis challenge: Variants of unknown/uncertain significance (VUS)

The most important challenge mentioned by the selected articles was that of the lack of standards and the complexity of variants interpretation, along with the high risk of finding VUS, which Sutton *et al*, 2012 consider a 'plague' to the field of clinical WES [190]. Unlike targeted single gene or gene panel sequencing assays, WES usually generates a long list of mutations, a large number of which have no known significance. VUS are reported to represent the majority of variants identified by next-generation sequencing (NGS) technologies such as WES[179,191], although much fewer VUS are found in WES than in WGS[192]. It is unsurprising that VUS is the most consistently reported challenge, as it lies at the heart of a network of connected challenges. The assessment of VUS pathogenicity is a long, complex and expensive research process[193], which requires the collaborative intervention of different highly trained specialists[194] including bioinformaticians, biologists and clinicians[195]. This need for interdisciplinary collaboration, along with the way WES testing may challenge existing professional roles in the clinic, was reported as a challenge by 50 (34%) articles. To interpret variants, these specialists rely on bioinformatics analysis pipelines made of imperfect algorithms [177,178,183,196], referring to imperfect databases[185,191,197,198]. The need to develop more efficient and standardised bioinformatics tools to filter, analyse and interpret WES variants was reported as a challenge by 44 (29.29%) articles. The need to share NGS results and to develop more complete, less biased databases containing fewer false positive and false negative variant-phenotype associations was identified as a challenge in 40 (27.2%) articles. As described by Jongbloed *et al*, [199] the "only reasonable way to deal with [the ascertainment of VUS] is to pursue maximum data dissemination in the scientific community", who could accelerate the analysis of VUS by creating and sharing access to large scale databases gathering sequencing results from as many studies as possible. Certainly, the more sequencing results are shared, the less likely it is that variants identified in patients will never have been reported before. This vision is also shared by Xue *et al* [191], who assert that "With more individuals from different ethnic groups sequenced through NGS, more rare variants will inevitably be revealed", and by Lin *et al* [200]: "Sifting through the millions of variants in an individual's genome for the pathogenic mutation seems to be the most urgent task at hand. The creation of dedicated databases specifically for the purpose of clinical interpretation based on NGS results from a large number of normal controls and diagnosed patients will significantly help this endeavor". Considering the current uncertainty

involved in interpreting VUS, they can represent a heavy burden[201] if reported to a patient's genetic counsellor or physician. Having access to this information may force clinicians to make a 'judgment call'[202] in trying to interpret VUS, and potentially report them to patients, which risks causing them unnecessary anxiety[203]. This dilemma is particularly prevalent in screening for mutations contributing to the genetic background of rare diseases. Indeed, some genes are only found to be mutated in 1 or 2 families in the world. It is therefore very difficult to estimate their pathogenicity and their exact impact on patients, which also makes genetic counselling significantly more challenging[204]. According to Rabbani *et al* [205], this should be carefully addressed in the consent form, and discussed consent process. In Need *et al* [176], the decision was taken at the onset of the study to not report any variants of 'uncertain significance' to the patients, regardless of whether or not they were later proven to have significance. In comparison, Ream *et al* [206] performed a pilot study in which the need to explain VUS to the families of 6 pediatric drug-resistant epilepsy patients represented a significant challenge, which led them to conclude that "WES may raise more questions than it answers for some patients".

2.4.2.2 Incidental findings

The challenge of IF was also consistently mentioned in 92 (53.7%) of selected articles. IF can here be defined as information of clinical relevance which is found during the WES data analysis and which is beyond the scope of the original clinical condition for which the patient was 'prescribed' a WES test. According to Sankaran *et al* [198], the "identification of actionable, IF during genome-wide DNA sequencing genetic studies is a major concern of many patients, as well as health care providers", and this can "cause ethical and clinical dilemmas" [207]. The topic of genomic IF is heavily discussed in the literature, and two recently published reviews [208,209] provide strong evidence showing that there is a lack of consensus on how to define, analyse, and report such variants to patients and research participants. Within our selection of articles, for instance, Lyon *et al* [210] consider the term "IF" to be "misleading". They prefer using the term "secondary findings", which they argue better represents their importance and could help correct the view that such findings do not require significant time and effort to be analyzed, interpreted, and reported. In 2013, Sankaran *et al* [198] stated that there was no consensus on just how frequently they are actually found in NGS data. However, several authors provide different estimates: in 2014, Xue *et al* [191] provided references to support the claim that "the rate of

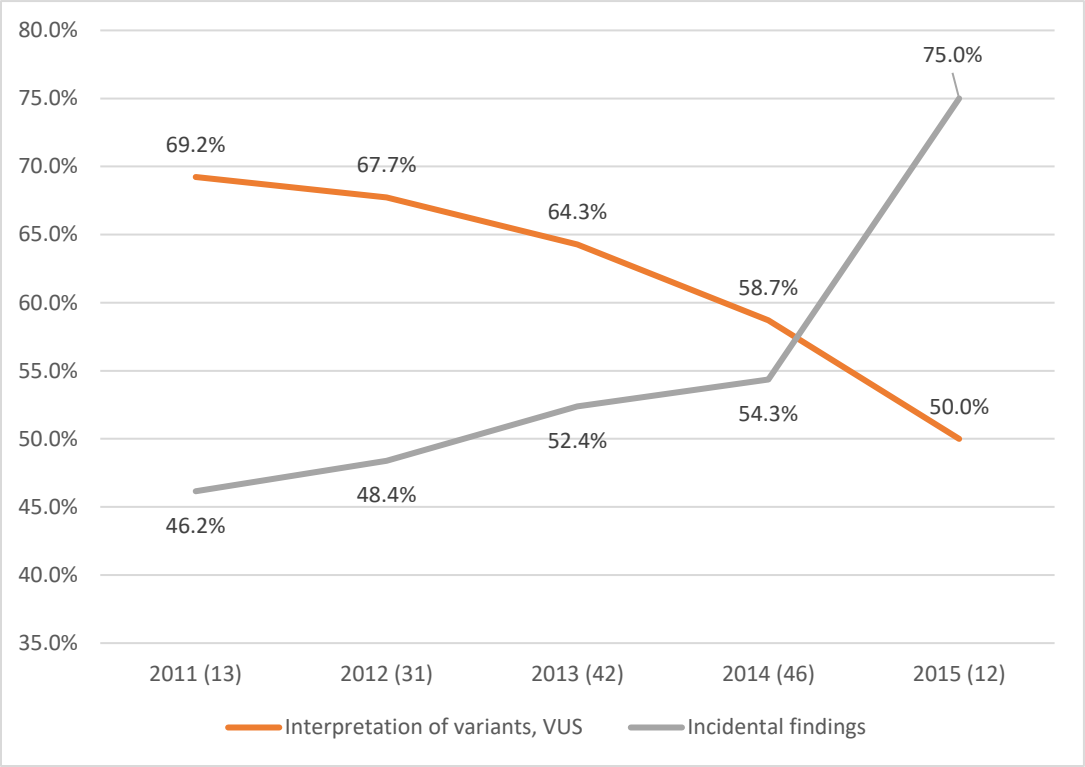
reportable IFs can range from 1 to 8.8%", while Gecz *et al* [211] argued that they range from 1 to 2% of patients. Regardless of how often IFs are found in practice, they have to be addressed in the patient pre-test counselling process [192,212], and this 'intensive genetic counseling' [170] can be a "main issue" in practice [181,213]. Incidental findings are viewed as a potential "additional burden"[206] and source of anxiety for patients and their families [203,214,215].

19 out of the 55 articles published since 2013 which mention IF as a challenge (34.5%) refer to the American College of Medical Genetics and Genomics (ACMG) recommendation on reporting IF [158,163]. This recommendation, which provides a list of 56 genes to be systematically searched for 'actionable variants', has clearly raised "concerns"[194] and debate on this topic rather than helping to resolve it. Even after mentioning these recommendations, articles published in 2014 refer to the reporting of IF by clinicians as "currently a subject of intense debate" [193], "one of the current, contentious debates"[214], or state that "there remains strong debate"[197] and an "ongoing discussion on how to best proceed with incidental findings"[216]. Malhotra *et al* [183] specifically mention that "the methods of providing [incidental findings] to patients are not entirely clear, although some recommendations have recently been made by the American College of Medical Genetics and Genomics". Even in 2015, this is still considered to be a "current debate" by Goldberg *et al* [217], and Bender state that the discussion of this topic "will undoubtedly continue"[218]. This uncertainty on how to define and report IF is described as the justification for using targeted testing over WES and more generally NGS in certain clinical contexts, such as hematology [187] or for heart diseases [219]. The challenge of IF even leads Lohman *et al* [216] to refer to WES and WGS as a "curse" as well as a "blessing".

From 2011 to 2015, we noted a steady increase in the proportion of selected articles discussing the challenge of IF. Indeed, it rose from 46.2% of articles published in 2011, to 75% in 2015. This trend is opposed to that of the proportion of articles discussing VUS, as displayed in **Figure 2.5: proportion of articles addressing VUS and IF per year**. Since the total number of selected articles published per year is variable and relatively small, it is difficult to attest the significance of this trend. However, we can make the following hypothesis: as software tools and reference databases have improved, the interpretation of WES variants has become less and less challenging for technology users. On the other hand, the publication of recommendations and guidelines in the USA [158], Canada [165] and Europe [164] has polarized the debate on the challenge of

identification, classification and reporting of IF, which may help explain why it was increasingly mentioned in our selection of articles.

5) Figure 2.5: Proportion of articles addressing VUS and IF per year



Legend: in parenthesis next to the year of publication of articles, we indicated the total number of selected articles published that year.

2.4.2.3 Cost and reimbursement

The challenge of WES' cost and of test reimbursement is reported in 49% of articles (72). It includes a number of sub-challenges along the WES data trajectory from production to analysis and interpretation. Although they do not provide much detail, a number of articles published in 2014 and 2015 consider that WES is still too expensive to be implemented as a standard of care in different contexts such as epilepsy [195], acute myeloid leukemia [193], axonopathies [220], sudden unexplained death [221] and cardiac arrhythmia [219]. Since sequencing costs have fallen drastically over time, it is notable that even in 2014 some authors consider that it is the sequencing itself that is too expensive [178,222–224]. Other justifications for the high price of these tests mentioned by

authors include the cost of data storage [225] and necessary Sanger validation of WES results [191]. Data interpretation in general is another reason provided to explain the higher costs of WES compared to more targeted sequencing [191,226,227]. Focusing on the possibility of using WES in newborn screening, Beckmann *et al* [228], provide a more detailed assessment of costs which leads them to conclude that "From a cost perspective, generalization of this practice with current procedures would entail a monumental effort that is likely to ruin our social healthcare programs." Those "important social, economic, and human costs" are linked to the increased time clinicians would have to spend interpreting and reporting WES results to patients and families.

The large-scale application of WES in the clinic will only be possible if it is integrated fully into the healthcare system as a standard of care for certain conditions. This requires a thorough economic evaluation of possible sources and strategies to reimburse this sort of analysis. According to many articles from the USA, UK and Germany published after 2014, cost assessment analysis and economic evaluation studies will still have to be performed in order to formally establish the relative cost efficiency of WES compared to other techniques [175,179,206,214,216,229,230]. The need for private insurance providers to reimburse these tests is reported as one of the key elements standing in the way of clinical implementation of WES on a larger scale, especially in the USA. [180,192,230–232]. Not only will the clinical utility [203] and cost efficiency of these tests have to be proven, but insurance companies and the public healthcare system will have to organise the administrative infrastructure needed to reimburse those tests, such as by creating 'new billing codes'[180,233].

2.5 Discussion

Our methodology carried a number of limitations. The first challenge of our approach is that we tried to identify elements in publications which had a different primary focus. Indeed, we were looking to identify sections describing unsolved implementation challenges in publications focusing on the description of the actual use of WES in a clinical context. This made the task of identifying those sections more difficult, and may have resulted in failure to identify a number of articles. Indeed, the relevant sections of the selected articles were extremely diverse, ranging

from a few words to full titled sections. Another issue which could possibly have led us to miss relevant publications was our choice of search terms. Our keyword combination of ("Clinical application" OR "Medical application" OR "Healthcare" OR "Clinical care" OR "Medical care" OR "Clinical practice" OR "Clinical diagnostic" OR "Medical practice") may have lacked specificity, leading us to overlook relevant articles because of the very high number of hits we obtained. In addition, the process of filtering all 2095 articles was very lengthy. Since the date at which we performed the search, a number of potentially relevant articles have been published. In addition, the regulatory landscape of clinical WES has evolved, with the publication of a number of guidelines and recommendations which will significantly impact this field, notably in Europe[234], and the USA[235–238]. The speed, efficiency and reproducibility of the data filtering process could be significantly enhanced if this process was partly automated. However, to our knowledge there is no open access software tool that could have performed the search based on keywords and context generation more efficiently than we did. One other limitation lies in the combination of quantitative and qualitative approaches we used to analyse all 23 challenges identified in 147 selected articles. This was a relatively small sample size in which to obtain significant differences between sub-groups of articles. On the other hand, it was a high number of articles to analyse thoroughly, which is why we decided to analyse only the challenges that were most reported by authors. We believe this combination of qualitative and quantitative methodologies is key to making informed policy decisions based on the latest body of evidence regarding technologies such as WES.

2.6 Conclusions

A number of challenges need to be resolved before whole exome sequencing can be implemented as a standard of care in the clinical setting. Through this systematic review of the literature, we could identify as many as 23 of these challenges. The three challenges that were most consistently reported by technology users were that of incidental findings, variants of unknown significance, and the cost of the technology. Although a small number of challenges, notably communication with patients, education of clinicians, and patients' turnaround time, were reported differently in articles focusing on cancer, rare diseases or all diseases, and in articles from different countries, most challenges were discussed similarly across diseases and

countries (data not shown). WES is already used in the clinical setting, and may soon be considered the standard of care for specific medical conditions, most notably for the identification of mutations contributing to rare genetic diseases. Clinics in the USA[182], France[81] and the Netherlands[239] already report promising results from the systematic use of NGS in hundreds of patients. Yet technology users are calling for certain standards and guidelines to be published before this technology replaces more focused approaches such as gene panels sequencing. In addition, it is clear that a number of infrastructural adjustments will have to be made for clinics to store, process and analyse the amounts of data produced by WES. The interpretation of this data requires specially trained staff, and patients and families must also be adequately prepared to deal with WES test results. Some intermediary solutions may be found, such as the one suggested by Topper *et al:* "In the near term, we suggest that many of these technical and ethical challenges may be alleviated by a targeted analysis approach, in which the full exome sequence is generated in patients, but analysis is initially limited to those genes already known to play a role in the presenting disorder"[201].

2.7 Competing interests

The authors declare that they have no competing interests.

2.8 Acknowledgements

We thank Anne Cambon-Thomsen, Bartha Maria Knoppers, David Rosenblatt and Ma'n Zawati for their guidance in developing the study design. We also thank Derek So for his help on the manuscript, and, Simon Papillon-Cavanagh and Sébastien Lamy for their help with the statistical analysis of the data.

CHAPTER 3: PEDIATRIC LITERATURE ANALYSIS

Preface

The reasons for us to focus on the pediatric context in Chapter 3 were threefold: In Chapter 2, we realised that most of the patients that had received NGS tests in the context of their care were children. In addition, at this point we had also identified the teams we would work with in Chapter 4, for our multiple case study analysis. In these teams too, the great majority of patients undergoing NGS tests were children. Finally, the pediatric population is a particularly vulnerable one. Decisions are often made on their behalf by parents or legal guardians, who often experience that they have to balance the present and future interests of their child, while taking into account their own short and long-term well-being, and family dynamics. One of the themes we explored in Chapter 3 is therefore notably the right of the child to an open future[240,241], which may be particularly challenging to respect and protect when receiving genetic results[242–245] which have an impact on the future health status of both the children and their parents. For these reasons, we sought to extract articles selected in Chapter 2 which specifically focused on pediatric patients, or discussed issues that are specific when offering NGS to children.

Another element we wanted to explore further was the impact of existing policies and regulations, and the overall awareness of technology users about these documents. Indeed, many authors in the publications analysed in Chapter 2 called for the publication of more guidelines on the clinical use of NGS technologies. However, we realized that many of such guidelines or position statements were already published at the time authors complained about their absence.

Specific authors' contributions (not described in the published manuscript):

- Gabrielle Bertier designed and performed the literature search and initial analysis, produced the first manuscript draft, managed the manuscript master document integrating comments from co-authors, as well as the submission, revisions and contact with the editor.

- Karine Sénécal performed the search and initial analysis of guidelines, contributed to the analysis methodology, and contributed to the results and discussion sections.
- PB provided guidance on the analysis methodology and commented on the full manuscript.
- DV provided guidance and contributed to the analysis design, results and discussion sections.
- All authors read and approved the final manuscript.

The manuscript was published in Critical Reviews in Clinical Laboratory Sciences in 2017 and is available at the following link:
https://www.tandfonline.com/doi/full/10.1080/10408363.2016.1275516

UNSOLVED CHALLENGES IN PEDIATRIC WHOLE-EXOME-SEQUENCING, A LITERATURE ANALYSIS

Gabrielle Bertier, Karine Sénécal, Pascal Borry, Danya F Vears

Gabrielle Bertier
(Corresponding Author)
gabrielle.bertier@mail.mcgill.ca
McGill University, Human Genetics Centre of Genomics and Policy 740 Dr Penfield avenue Montreal, QC, CAN H3A 0G1
+1514398895

Karine Sénécal
karine.senecal@mcgill.ca
McGill University, Department of Human Genetics Centre of Genomics and Policy 740 Dr. Penfield avenue Montreal, QC, CAN H3A 0G1
+15143988038

Pascal Borry
pascal.borry@kuleuven.be
KU Leuven, Centre for Biomedical Ethics and Law, Department of Public Health and Primary Care, Kapucijnenvoer 35, Leuven, BE 3000
+3216379517

Danya Vears
danya.vears@kuleuven.be
KU Leuven, Centre for Biomedical Ethics and Law, Department of Public Health and Primary Care, Kapucijnenvoer 35, Leuven, BE 3000
+3216374685

3.1 Abstract

Whole-exome sequencing has been instrumental in discovering novel genes and mechanisms causing Mendelian diseases. While this technology is now being successfully applied in a number of clinics, particularly to diagnose patients with rare diseases, it also raises a number of ethical, legal and social issues. In order to identify which challenges are foreseen directly by technology users, we performed a systematic review of the literature. In this paper, we focus on recent publications related to the use of WES in the pediatric context and analyze the most

prominent challenges raised by technology users. This is particularly relevant considering that a) most patients currently undergoing testing using WES to identify the genetic basis for rare diseases are children, and b) their lack of capacity to consent for themselves makes them a vulnerable population and generates the need for specific ethical, legal and regulatory procedures. We identified key challenges which related to four main categories: 1) intake, 2) sequence production and analysis, 3) reporting of results and counselling considerations, and 4) collaborative data interpretation and data sharing. We then contextualize these challenges in light of the recent recommendations and guidelines published by professional societies, which have significant potential to impact the field.

3.2 Keywords

Whole-exome-sequencing, Technology users, Pediatrics, Children, Ethical, legal and social issues, Unsolved challenges

3.3 Introduction

Recent developments in genome-wide sequencing technologies have revolutionised genomic research and represent a major innovation in the diagnosis and treatment of many disorders, particularly rare diseases and cancer. Genomic sequencing has been instrumental in uncovering novel genes and mechanisms causing Mendelian diseases. Given that the capture, sequencing and analysis of most protein-coding parts of the genome (whole-exome-sequencing or WES) only appeared in the research arena around 2011, genomic sequencing technologies have had an incredible impact on our knowledge of human genetic diseases over a very short time frame [246]. Since then, this technology has entered the clinic [81,179,181]. While WES generates significant hope for patients to end their 'diagnostic odyssey' more quickly and at a lower cost [81,179], this technology, as well as other genomic sequencing methods, raises a number of ethical, legal and social issues [140,182].

In order to identify which challenges are foreseen directly by technology users (medical doctors, life science researchers or medical researchers directly exposed to the technology in their field of

expertise), we performed a systematic review of the literature [1]. While that review aimed to give a general overview of all issues in any clinical context, in this paper, we focus specifically on the most prominent challenges identified in recent publications related to the use of WES in the pediatric context. This is of particular relevance considering that most patients undergoing testing to identify the genetic basis for rare diseases are children, and that their lack of capacity to give consent has generated specific ethical, legal and regulatory procedures [139,247].

3.4 Methodology

The systematic literature review methodology we employed was adapted from the PRISMA guidelines [166] and the Petticrew and Roberts practical guide [167]. We performed our search in six databases: EBSCO (academic search complete), EMBASE, NCBI Pubmed, Science Direct, Scopus and Web of Science. Our first objective was to identify all the possible challenges associated with the clinical application of WES, as reported by technology users. Therefore, the complete search string used was the following: ("exome sequencing" OR "whole-exome sequencing" OR "whole exome sequencing") AND ("Clinical application" OR "Medical application" OR "Healthcare" OR "Clinical care" OR "Medical care" OR "Clinical practice" OR "Clinical diagnostic" OR "Medical practice") [1]. Here, we focus our analysis on themes of relevance in the context of pediatrics.

The full text of articles and reports were initially searched without any date or language restriction. The search resulted in 2275 articles, which we filtered down to 2094 after removing duplicates, any non-peer reviewed journal articles, and articles not written in English, French or Spanish. Two researchers then independently filtered articles using four inclusion criteria: 1) articles were written by a technology user (defined as a medical doctor, life science researcher or medical researcher directly exposed to the technology in their field of expertise); 2) articles specifically addressed WES (including those which addressed whole genome sequencing or gene panels in addition to WES); 3) articles included considerations on the clinical implementation of WES; 4) articles listed challenges relating to this clinical implementation which were unsolved. Articles were excluded if they were authored by researchers in policy or human and social sciences, only considered WES in the context of basic research or discovery, or only listed challenges which were considered by the authors to be solved, or easily solved through measures

already in place. 147 articles remained for analysis after applying these criteria. Criteria 3) and 4) each resulted in the removal of more than 500 articles. Because we used a broad search strategy, many of the articles either only cited WES as a technology that can be used in the research context, or did not report any specific issues relating to clinical implementation of the technology.

Subsequently, the subset of "pediatrics articles" were selected if the patients undergoing whole-exome sequencing in the paper were children, or the article discussed specific challenges linked to the use of the technology in a pediatric setting. Finally, to isolate challenges that are likely to remain unsolved, given the rapidly progressing nature of the field, we selected only the articles that were published in 2013 or later. This resulted in a total of 26 articles. The results of all of the screening and filtering steps are described in Table 3.1. Inductive content analysis was then used to analyze the articles, where categories of unsolved challenges were identified inductively from the articles, rather than being predetermined [169].

5) Table 3.1: Screening and filtering process.

	Total	**Removed**
Total Articles	2275	
Removing duplicates	2094	181
Peer reviewed journal articles	1810	284
Written in English, French or Spanish	1805	5
Accessible	1792	13
Included in general systematic review	147	1645
"Pediatrics articles"	60	87
Published in 2013-2015	41	19
Included in Pediatrics review (mention pediatric issues)	26	15

3.5 Results

In our selection of articles, we identified a total of 14 categories of unsolved challenges which related to the use of WES in the pediatrics population. The full list of categories can be found in Table 3.2. While these categories refer to aspects which span the entire WES process, we have grouped these categories into four overarching themes: 1) intake, 2) sequence production and

analysis, 3) reporting of results, and counselling considerations, and 4) collaborative data interpretation and data sharing. The content of these categories from the articles is summarized below.

6) Table 3.2: List of identified unsolved challenges in pediatric Whole-Exome-Sequencing

Themes	Categories
A. Intake	1. Patient selection 2. Turnaround time
B. Sequence production and analysis	3. Data storage 4. Quality control 5. Bioinformatics processing
C. Reporting of results, and counselling considerations	6. Communication with patients and families 7. Pre and post-test counselling 8. Pre-natal options 9. Variants of Unknown Significance 10. Incidental Findings
D. Collaborative data interpretation and data sharing	11. Databases and Data sharing 12. Collaborative interpretation 13. Genetic discrimination 14. Privacy

3.5.1 Intake

When implementing WES in a clinic, often the first question is which patients will most benefit from the test, and should therefore be offered WES? This is still debated in the scientific literature, and is clinical context-dependent. In our selection of articles, authors discuss different approaches to the selection of pediatric patients who undergo WES. While some argue that it should be offered to any undiagnosed patient, regardless of their condition [248], others propose a more selective use of WES, either through a formal set of criteria [249], or by allowing clinicians to decide which patients would benefit from testing [172]. Biesecker and Green discuss how if the decision is left to the clinician, it is important that they have a good understanding of which patients will most benefit from the test [249]. There is also debate as to whether sequencing should be undertaken using trio analysis, where the affected child and also both parents are sequenced, or just the proband [214,248,250,251]. Although the production of sequencing data for trios is three times as expensive, it allows rapid identification of de novo mutations in the proband. Therefore,

this approach may be particularly valuable in cases where there is a strong suspicion that the causal mutation appeared de novo in the affected child [175], or that it has a recessive mode of inheritance [150,185,249]. In the reported articles, the diagnostic yield of WES in undiagnosed patients ranges from 16% [181] to 45% [252], but is usually between 25 and 30% [79,81], which is already higher than conventional testing [253]. The success rate of such testing is likely to be dependent on the screening strategy used and the level of clinical phenotyping undertaken on the patients. This presents a challenge, as not all clinicians will have the necessary training in genetics, nor the time to synthesize the most recent literature on this technique in order to determine the most appropriate testing strategy [196,254].

Aside from determining the most effective screening strategy, the pre-test counselling required to explain WES to patients and their family presents another likely challenge for clinicians [218,222,228]. According to various authors, medical professionals responsible for obtaining consent from the patient or their family may need special training to effectively communicate information about the possibility of receiving uninformative results, uncertain results, or incidental findings that may be identified through WES in order ensure they make an informed choice about undertaking the test [218,222]. Due to the complexity of these pre-test discussions, the time constraints of the clinician were seen as an additional factor inhibiting their ability to obtain truly informed consent [228]. This may be particularly challenging in the context of pediatric patients [248] whose parents have to decide whether to undertake WES on their children's behalf when some of the findings may have more relevance for themselves than for the immediate health of their child [206,214,255].

3.5.2 Sequence production and analysis

According to various authors, in order for WES to be offered in a standardized manner, formal guidelines, including strict quality control measurements, must be published [231,256]. While some have called for this regulation to be provided by the Food and Drug Administration (in the USA) [256], this may be challenging for regulators given the amount of data to be analyzed from a whole exome (about 30 million base pairs, or 1% of a whole genome) [248]. Bioinformatics pipelines, which filter the many thousands of variants found in each patient’s exome [192,255], are often developed in the context of research, where the purpose is to identify novel variants or disease-causing genes, and need to be adapted to interpret data in the clinical context [222,227]. The process

of sequencing, analysis, interpretation, and Sanger validation of WES results is time consuming, and can last several months [232], although this has been reduced to 1-2 weeks [257]. Lengthy turnaround times from sample collection to the reporting of results can be problematic in the clinical setting, as described by a number of articles in our selection [175,222,227]. For example, this may be of critical importance for parents in contexts such as prenatal testing, where decisions to proceed with or terminate a pregnancy may be awaiting results from WES [175]. Improvements in bioinformatics tools are required to aid data interpretation and increase the speed of analysis [175,222,227]. In addition, as the process of filtering WES variants to uncover causal or clinically targetable variants is often dependent on access to large repositories and internationally established databases, sharing of linked genotype-phenotype data between laboratories in ways that are curated and easily searchable is essential to improve the interpretation of variants [41,216,222].

3.5.3 Reporting of results and counselling considerations

WES generates a high number of variants [206]. Some of these variants may be of unknown significance at the time of the test (VUS), either because the function of the gene is unclear or the pathogenicity of the variant has not been established. Other variants identified may be clearly pathogenic but their function may be unrelated to the condition under investigation (incidental findings, or IFs). Both VUS and IF make the reporting of WES results to patients more challenging than the clear-cut results one may get from a more targeted approach.

In the study by Ream and Macklin, VUS that "had to be considered and explained to the family" were identified in all six patients who underwent genetic testing using WES [206]. The challenges associated with interpreting and reporting VUS to patients leads the authors to conclude that "WES may raise more questions than it answers for some patients" [206]. Indeed, Grody and colleagues estimate that most of the 18,000 variants found in every whole-exome sequence will be VUS [255]. Given this preponderance of VUS, three of the papers discuss the notion of regular reanalysis of VUS found in patients [182,214,249]. Jiang and colleagues suggest that this re-evaluation should be offered to patients as part of comprehensive care and patient follow-up [214]. However, Biesecker and Green explain that the potential for a "negative result" to become "positive" or clinically relevant can complicate the post-counselling process [249]. In the study published by Jacob and colleagues, patients were offered the option to have their data reanalyzed. This

significantly impacted their bioinformatics pipelines, altered decisions regarding data storage, and increased their overhead costs. Although Biesecker does not provide a solution as to how these issues can be resolved, they postulate that: “The methods and approaches for ongoing reanalysis of CGES [Clinical Genome and Exome Sequencing] results have not been established, but it should eventually be possible to regularly reanalyze such results with the goal of identifying previously unknown variants.” [249].

In addition to VUS, incidental findings that are unrelated to the phenotype of the patient can also be found in WES data. Concerns about identification of these IFs are often related to their potential to create anxiety in patients if reported, and lead to costly follow-up procedures. Within our selection of 26 articles, nine reported that IFs, and the reporting of such results to the patients and their families, pose specific issues when the patients undergoing genetic testing are children. Three call for extra care in the handling of IFs when testing children using WES [218,250,258]. For example, one article which discusses the use of genetic testing in children with cardiomyopathies, asks for the development of “thoughtful strategies” to deal with IFs found in children, particularly when the disease has no known “effective preventive treatment” [250]. Neveling and colleagues, who performed post-hoc analysis of the diagnostic yield of WES compared to ‘traditional' testing in their clinic, reported that the main reason patients who received pre-test counseling refused to undergo WES was “concern regarding unsolicited findings, especially in children and young adults” [258]. Since the authors provide no further detail to justify their claim, it is difficult to assess how systematically this information was collected, and therefore how this information should be interpreted.

As is the case for other genetic tests, the information uncovered through WES is also of a familial nature, and may be of significance not only to the probands but also their parents. This is of particular importance when the test is offered in a prenatal setting, or if its results may impact future reproductive decisions [205,214,248,255]. Three publications mention concerns relating to the impact of IFs identified in children which are relevant to the health of their parents [194,214,227]. While one paper which focused on the context of prenatal diagnosis notes that identification of IFs not only has implications for the pregnancy, but also “may have significant implications for the health of the parent” [227], another paper seems to share similar concerns in the context of pediatrics [214]. According to Newman and Black [194], who focused on the use of WES in children

with epilepsy, IFs can be an 'additional burden' for parents, who are already 'burdened' by their child's illness.

Another three publications address the specific issue of identifying IFs related to late-onset conditions in children, and the impact that reporting such findings may have on the whole family [248,255,259]. This issue indeed raises "profound ethical concern", especially when the conditions are untreatable [260] and Kastanis and Katsanis [248] highlight this risk as an "additional ethical challenge" raised by pediatric genetic testing. The authors, in this publication from 2013, considered that there was still "no consensus" on how to report such findings. They provide evidence that while "genetic testing of asymptomatic minors for adult-onset conditions such as Huntington's disease" is "discouraged" by certain policies as it may have a negative impact on some children, other children react well to such results and only suffer from "minimal harm". [248] Interestingly, for Arboleda and colleagues [259], the risk of identifying IFs, especially in minors, in WES or whole-genome-sequencing strongly supports the use of more targeted genetic testing approaches and they state that "genetic testing for adult-onset diseases is ethically questionable in children, and under current guidelines [here authors refer to [261]] is only performed in exceptional circumstances". Grody and colleagues illustrate this problem through the example of a BRCA mutation identified in a 3 year old girl being tested for hearing loss or autism [255]. As these types of findings may also have implications for the entire family, not reporting these results may then engender a liability risk for clinicians, knowing that this could have an impact both on "the future health of the child or the present health of the parent who transmitted it" [255].

These articles highlight how the amount of data produced by WES and its intricacies complicates the task of medical doctors who have to obtain consent to perform WES, and then report results, which may also have implications for family members, for patients and/or their parents. After setting "realistic expectations" during pre-test counselling and consent [249,250], and mentioning the "risks, benefits and limitations" [230] of WES, clinicians have to explain to parents and families the potential for all the types of findings mentioned above (negative results, IFs and VUS, including their potential to become meaningful results over time). These additional results are likely to lead to longer, and therefore more costly, pre- and post-test counselling sessions. While the study by Jacob and colleagues allowed parents to choose which findings they want to receive following WES, this strategy is "not universally supported" [182]. As a result of this pre-test counselling session, some parents may indeed decide not to go ahead with WES for their children [262].

Another issue identified by two of our selected publications relates to the costs and reimbursement of WES tests. According to Berg [230], this has to be taken into account when deciding whether to offer WES to families: "[…] physicians should be judicious in considering when to obtain clinical exome sequencing; […] and should avoid unnecessarily burdening patients with the cost of such testing if not covered by insurance". Other authors [249] advise that the issue of cost be discussed during the counselling process, knowing that not all insurance providers will eventually reimburse the test even if prescribed by a doctor.

3.5.4 Collaborative data interpretation and data sharing

The most structural impact of genomic sequencing in the clinical setting is that of the need for a collaborative effort to interpret WES results. Some authors describe the need for a new kind of physician, who will be trained in several disciplines, including medicine, genetics and counseling [222,263]. Others either advocate for clinical geneticists to have a more prominent role in the clinical interpretation of data [255,264], or for several experts such as "molecular biologists, clinical geneticists, and bioinformaticists" to combine their efforts to aid data interpretation [255]. WES testing is no longer viewed as an individual physician's endeavor, and clinics offering genomic testing will need to adapt to this increased need for cross-disciplinary collaboration.

Authors also outline the need for WES data to be shared widely, either through clinical specialists or through large scale publicly accessible databases, to assist variant classification and identification of causative genes [216]. However, this creates additional challenges relating to protecting patients' privacy and preventing genetic discrimination [205]. This is particularly important in the context of pediatric care, where a breach of privacy may have long-term consequences on the child's future. If the child's carrier status for a late-onset debilitating disorder like Huntington's disease is revealed and shared [248], there are concerns it could be used against them in the context of insurance or employment [205]. Clinicians reporting pediatric patients' WES results may then be burdened with an ethical dilemma between their duty to inform patients and families about potential genetic risks for diseases (especially when preventative measures can be taken, like in the case of BRCA1 and BRCA2 mutations) and the risk for that information to be used against patients outside of the clinical care context.

3.6 Discussion

The results of our systematic review show that technology users reporting on the use of this technology did so mostly in the context of clinical research or "proof of concept" studies. This suggests that, to date, WES is still conceptualized as a clinical research endeavor rather than a standard of care test. Guidelines from governmental institutions and professional societies are being developed and amended as more evidence of analytical validity, clinical validity, and clinical utility of WES are produced by the scientific community. These guidelines are numerous, diverse, and emanate from a variety of institutions with different mandates, as evidenced by the identification of more than 15 guidelines in a review of the use of NGS in oncology in 2014 [265]. In this section, we will compare the challenges raised by technology users with how these challenges are addressed in guidelines published by three large professional societies: 1) American College of Medical Geneticists (ACMG), 2) European Society of Human Genetics (ESHG), and 3) Canadian College of Medical Geneticists (CCMG). The ACMG was the first to produce a specific guideline on clinical genome sequencing in 2012 [266]. They then produced a guideline on informed consent in 2013 [267] and an updated guideline focusing on reporting IFs [163]. The ESHG published general recommendations in 2013 [268] and recently released new statements [234] and the CCMG published a guideline focusing on NGS in monogenic diseases [165]. The last two documents were published after our literature search was performed and were therefore not available at the time articles in our review were published.

3.6.1 Intake

Our results showed that technology users have issues deciding which patients should undergo genomic testing such as WES, with some advocating for the use of WES in all undiagnosed patients, and others determining that testing should be restricted either according to specific criteria or based on the clinician's opinion. Author's views also diverged with regards to the most effective screening strategy (i.e. proband versus trios). The published guidelines do offer some criteria for clinicians on these challenges. To date, published guidelines recommend that WES be pursued only when other tests are not available or have failed to provide a diagnosis, and when the degree of genetic or phenotypic heterogeneity is high enough that this approach is more

practical or cost effective than standard techniques. Specific to children, in 2013 the ACMG recommended that genome and exome sequencing not be performed before the legal age of majority except for a) phenotype-driven clinical diagnosis; b) circumstances which will lead to early and effective monitoring or interventions; or c) institutional review board–approved research [267]. However, these guidelines are quite general, placing a significant degree of responsibility on physicians and clinical geneticists to make sound clinical decisions about which patients should receive WES. Indeed, the CCMG guidelines state "ultimately, the ordering physician's clinical judgment should prevail" in determining if to offer WES testing to a patient. They also caution that these tests should only be ordered by those with "sufficient expertise in use of the technology and clinical interpretation of the results" [165]. In contrast, minimal guidance is provided on the question of whether sequencing should involve trios versus proband only, with the CCMG guideline indicating that referring clinicians should discuss with the laboratory whether including parental samples, where available, is appropriate [165]. It is interesting to note that despite some of these recommendations being published in 2013, the technology users do not refer to them as potential solutions. It is unclear whether this is because they do not agree with the recommendations or whether they were unaware of their existence.

3.6.2 Sequence production and analysis

In our analysis, several authors mentioned the absence of formal guidelines for data processing and interpretation pipelines as an issue. Indeed, the issue of inconsistencies and variability in clinical results from different bioinformatics pipelines is of critical importance [41], as recently demonstrated by the Clinical Sequencing Exploratory Research (CSER) consortium, which published a comparison of the performance of nine different laboratories in the calling of a limited number of variants [237]. It is important to note, however, that efforts are being made towards producing standardized pipelines, particularly by the Centers for Disease Control and Prevention (CDC) [269].

Technology users noted that although progress has been made recently to increase the speed with which WES takes place [257], the turnaround time from sample collection to clinical results is still lengthy. Recently, Miller and colleagues have reported that a patient's whole-genome can be sequenced in as little as 26 hours [270]. However, such a rapid data production would be difficult to achieve in WES, knowing that technical steps unique to this technology such as exons capture

represent significant, unavoidable time. On the other hand, analysing and interpreting WES data is significantly faster than WGS, which comprises approximately 100 times more data [271].

By highlighting turnaround time as an unresolved issue, the technology users bring us back to the reality of the current limitations of the technology for some clinical settings and this is reflected in some of the guidelines. For instance, the ACMG 2012 guideline mentions that "prenatal diagnosis by genomic (i.e. next-generation whole-exome or whole-genome) sequencing has significant limitations" and that "[t]he current technology does not support short turnaround times, which are often expected in the prenatal setting." Other recent documents simply mention that turnaround time has to be considered when offering genomic testing [272,273]. While this puts a dampener on plans for WES and other genomic sequencing methods to be enlisted in newborn screening programs, the work being conducted in critically ill newborns by Stephen Kingsmore and his team at the Rady Children's Institute for Genomic Medicine suggests that it is only a matter of time before this issue will be solved [270].

3.6.3 Reporting of results and counselling considerations

Pre-test counseling was another unsolved issue identified by technology users in the pediatric setting. Similarly, all three sets of guidelines address this issue, specifying a list of aspects that should be discussed when counseling patients and their families, and conducting informed consent prior to WES. This generally includes a discussion of the expected outcomes of testing, outlining the potential benefits and risks of the test, the limitations of such testing, and the implications for family members. Information regarding the occurrence of VUS and possibility of IFs should also be discussed, together with the options to receive, or not receive, this information. The ACMG recommends that this should be done by a skilled professional, such as "a medical geneticist or an affiliated genetic counselor" [266,267] or "a qualified genetics health-care professional [...]" [163]. Similarly, the CCMG suggest consent be undertaken by a "qualified individual with a thorough understanding of clinical genome-wide sequencing" [165]. This consensual recognition of the need for formal and detailed consent to be obtained by highly trained genetic professionals in order to offer WES testing has a number of consequences. Access to such professionals may not be equally distributed in a given region, generating inequality in access between patients. Meeting this need is likely to require a significant long-term state investment in training, which may ultimately increase the turnaround time for testing.

The impact of such guidelines specifically on the pediatric setting is unclear. Access to clinical geneticists or genetic counselors capable of obtaining informed consent from parents to test their children is already part of routine care in clinics that offer genetic testing to children. Similarly, the fact that parents are responsible for deciding which test result to receive on behalf of their children is not portrayed as a source of debate in the guidelines, because this is not specific to new sequencing technologies.

3.6.4 Incidental Findings

Technology users discussed a number of different unsolved challenges relating to IFs in their publications, including their potential to lead to parental anxiety and costly follow-up procedures. Other commonly raised unsolved challenges related to how to manage IFs which had potential health implications for other family members, some of which may identify the child to be at risk of an adult onset condition. All three sets of guidelines provide similar recommendations regarding the handling of IFs. They indicate that, first and foremost, steps should be taken to minimize the risk for encountering IFs by focusing the analysis of WES data on a set of genes known to be involved in the disease being investigated. The limitations of the test and the potential to find IFs should be mentioned to patients during the pre-test counselling session. Detailed protocols are required, outlining how to handle IFs should they be identified, and the approach taken has to be shared at all levels, between data analysts, laboratory providers, clinical geneticists in charge of the case, ordering physicians, patients and families. If IFs are reported, there should be strategies to ensure patients and their families have access to any genetic counseling, preventative measure or treatment options required.

Specific to the pediatric setting, guidelines recommend that only variants which predispose the child and/or their family members to a serious condition for which prevention or treatment measures exist should be considered for reporting. Whether these should constitute a pre-determined list, such as that of the ACMG, or are considered on a case-by-case basis by the clinical team is guideline-dependent. However, variants which indicate a risk for a late onset condition for which no treatment or prevention measure exists should not be reported to parents. In addition, parents should have the choice to opt-out of receiving incidental findings, except those revealing risk for a highly penetrant condition that is medically actionable during childhood [165].

Although these consensual elements do provide some general guidance on how to approach the question of IFs, the details of implementation still need to be determined by laboratories or clinics offering genome-wide testing. This is particularly apparent in the 2013 ESHG document: "guidelines need to be established as to what unsolicited information should be disclosed in order to balance the autonomy and interests of the child and the parental rights and needs (not) to receive information that may be in the interest of their (future) family" [268]. This guideline also mentions that: "Patients' claims to a right not to know do not automatically over-ride professional responsibilities when the patient's own health or that of his or her close relatives are at stake." Here again, the responsibility for the "final call" lies with healthcare professionals, who some might consider to be best equipped to balance all the conflicting principles at stake in the decision to report or not an IF, such as the best interests of the child [274], parents' autonomy to make decisions on behalf of their children, and the right of the child to an open future [240,243]. Insights into how those professionals make these decisions have been highlighted in a recent review [275].

3.6.5 Variants of Unknown Significance

In the articles reviewed, a number of authors reported issues related to Variants of Unknown Significance, which are very likely to be found though WES. Because a VUS cannot be confirmed as benign and may therefore be related to the patient's condition, they can generate anxiety in patients. The assessment of their pathogenicity may require testing of other family members, or additional investigations, which may be costly and time consuming for patients and their families. In addition, authors also discussed the changing status of VUS and whether reanalysis of these variants should be considered as part of standard care.

Similarly to IFs, guidelines suggest that the risk of finding a VUS should be explained to patients during pre-test counselling, that laboratories should define a clear protocol should VUS be identified, and that this protocol should be shared with all relevant stakeholders. The guidelines also encourage laboratories to focus their analysis on a set of known genes in order to limit the risk of encountering VUS. This, however, would not prevent clinicians or laboratory technicians from encountering a previously unidentified mutation in a known gene, the effect of which is unknown.

Guidelines also specify that interpretation of variants should be done on the basis of current knowledge at the time of testing. Laboratories and clinics are encouraged to offer periodic re-analysis of patients' data only if they consider this is manageable considering their storage and patient management capacities. However, the ESHG states that if at some stage either the laboratory or a community of experts decide to change a variant from one class to another, the laboratory carries the responsibility of reanalyzing the data, re-issuing any reports required and ensuring referring clinicians are informed [234].

3.6.6 Data sharing

Technology users highlighted the need for systematic and generalized sharing of variant data from WES to enable the advancement of research, and enhance the detection of genetic causes of disease. However, they acknowledge the additional challenges this poses in relation to protection of patients' privacy and against discrimination, both of which are particularly important in the pediatric setting. All three sets of guidelines recognize the importance of data sharing, with the recent ESHG guideline recommending that all reported variants be added to "federated, regional, national, and/or international databases", including variant frequencies in healthy individuals. Although they are imperfect [41], and do not always allow for submissions by non member organisations or individuals, a number of such databases are already in place and highly used, such as ClinVar[a], the Human Gene Mutation Database (HGMD)[b] and Phenome Central[c] for affected patients, and 1,000 genomes project's International Genome Sample resource[d], dbSNP[e], the Exome Variant Server[f], the Exome Aggregation Consortium (ExAC)[g] and the Genome Aggregation Database (gnomAD)[h] for controls.

---

[a] https://www.ncbi.nlm.nih.gov/clinvar/
[b] http://www.hgmd.cf.ac.uk/ac/index.php
[c] https://www.phenomecentral.org/
[d] http://www.1000genomes.org/data-portal/sample
[e] http://www.ncbi.nlm.nih.gov/SNP/
[f] http://evs.gs.washington.edu/EVS/
[g] http://exac.broadinstitute.org/about
[h] http://gnomad.broadinstitute.org/

However, all these guidelines recommend consent be obtained prior to the use of patient data in research, with the CCMG suggesting the risk for breach of privacy and genetic discrimination be discussed during pre-test counselling [165]. In recent years, significant progress has been made in this domain, and a number of large scale international data sharing initiatives have been launched to systematize the sharing and reporting of patients' variant data. Of particular relevance to the field of rare diseases is the "matchmaker exchange" [76,276], which aims to create a federated platform which includes large scale databases such as Phenome Central[c] and DECIPHER[a] to enable easy match-making between clinicians who are caring for undiagnosed patients with similar phenotypes or genotypes. In the pediatric context, where consent is obtained from parents on behalf of their children, the question of whether the decision to participate in research can be reverted when the person reaches the age of majority remains unsolved.

3.6.7 Limitations

Our methodology has several limitations. We filtered the articles relevant to pediatrics for analysis at the final step of the literature review and therefore our search terms were not specific to this field. However, we believe this enabled our search to be as comprehensive as possible. We also chose to focus our search on articles published by technology users because we wanted to understand which issues they experienced, and which challenges they reported as being unsolved to date. Further review of the challenges discussed by other stakeholders, such as ethicists, legal scholars or patients would also be warranted. Although our search focused on WES, we believe that our findings are relevant to other genomic technologies such as WGS.

3.7 Conclusions

The results of our systematic review indicate consensus among the technology users about some of the core unsolved challenges related to the use of WES in the pediatric population. As we have shown, many of those challenges are addressed, at least to some extent, by guidelines published by professional societies on this topic. However, a significant degree of responsibility

[a] https://decipher.sanger.ac.uk/

remains on the shoulders of professionals, many of which are the kinds of technology users who published the articles included in this review. This allows professionals to make key decisions to enable the clinical implementation of WES and NGS in the local context and based on their clinical judgment and experience. However, this kind of experience takes time to accumulate and so far only a small number of clinics have implemented WES based testing as part of their routine practices. We foresee that in the near future, a number of different models for implementation of clinical NGS will coexist and that more detailed guidelines will be established once more evidence data is collected on a number of indicators, including diagnostic yield, patient outcomes, and patient preferences.

3.8 Funding details

This work was supported by the Research Fund Flanders (Belgium) and the Ministère de l'Économie, de la Science et de l'Innovation du Québec (Canada), (Grant Number : PSR-SIIRI-850) and the Fonds de recherche du Québec (Réseau de Médecine Génétique Appliquée du Québec – RMGA).

CHAPTER 4: MULTIPLE CASE STUDY ANALYSIS

Preface

In this chapter, we aimed at answering our second research question: How are patients' NGS data currently managed (produced, accessed, analysed, and shared) in clinical institutions in Quebec and in France?

The value of collecting and analysing "real-world" evidence, notably from practitioners and technology users has been recognised as fundamental in the field of genomics[20,277], and crucial in order to design stable, efficient and responsible policies which are adapted to the specificities of the local implementation context[6]. In Chapter 3, we also found that most policies published to date left key decisions in how to use NGS in the clinic in the hands of clinicians and professionals, based on their experience and knowledge of patients and families. This is why we sought to interrogate technology users and practitioners, in order understand why and how they put in place the technology, and the choices they made to use it for the benefit of patients. Most studies published to date are based on surveys or interviews, which may not provide a comprehensive picture of the context of genomics implementation as it evolves in time. The case study method on the other hand, requires the researcher to slowly build a relationship of trust with the teams, to observe the daily conduct of their activities overtime, and collect more granular evidence than that which can be collected with a short interaction with an interview or a survey[278–281]. This method therefore allows the researcher to uncover and describe elements such as inter-personal dynamics within teams, or conflict or tensions with external stakeholders[282] which may be crucial in understanding how technologies are successfully or unsuccessfully implemented[283]. We designed the interview guide based on the challenges identified in Chapters 2 and 3. (details in Appendix C, Additional file 1). The case study method is also extremely challenging, because of the length of data collection, which took place over the course of 1.5 years, from November 2015 to July 2017 (details showed in Appendix C, Additional File 2). We faced another series of challenges in reporting our results. Indeed, the ethics approval we obtained in one institution in Quebec required that its name remain confidential. This prevented

us from presenting any result which could potentially identify the institution, and from providing this institution's ethics approval. (Other ethics approvals are provided in Appendix C, Additional file 4). Finally, since the narrative description of the results we obtained was lengthy, we decided not to submit all results in one publication. Results on the research/clinic boundary were explored further in Chapter 5. Additional findings which were not submitted for publication are also presented in Appendix C, Additional file 3).

Authors contributions (not detailed in the manuscript)

- Gabrielle Bertier was the point of contact with all four team leaders, and all team members. She designed the first version of the interview guide. She conducted and recorded all interviews, which were transcribed verbatim through a professional service. She conducted all observation work (participation to meetings). She collected all documents from team members. She logged all collected data into NVivo and conducted the analysis. She produced the first draft of the manuscript, and managed the manuscript submission, revisions and contact with the editor.
- Yann Joly was the main applicant to obtain ethics approval to conduct the study. He was involved in study design and revised the interviews questionnaire. He also revised the manuscript.
- Both authors read and approved the final manuscript

CLINICAL EXOME SEQUENCING IN FRANCE AND QUEBEC: WHAT ARE THE CHALLENGES? WHAT DOES THE FUTURE HOLD?

Gabrielle Bertier[1,2*], Yann Joly[1]

1. Centre of Genomics and Policy, McGill University Department of Human Genetics.
2. Université Toulouse III Paul Sabatier and Inserm UMR 1027

* Corresponding author

Gabrielle Bertier
Centre of Genomics and Policy, McGill University
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1, Canada
Tel : +1 514-398-8957
gabrielle.bertier@mail.mcgill.ca
-
UMR 1027, Inserm, Univ Toulouse III - Paul Sabatier
37 allées Jules Guesde F-31000 Toulouse, France

Yann Joly, PhD, Ad.E.
Research Director, Centre of Genomics and Policy, Assistant Professor, Department of Human Genetics, McGill University, Faculty of Medicine
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1 l Canada
Tel: +1 514-398-7286
yann.joly@mcgill.ca

4.1 Abstract

Background: The decreasing cost of next-generation sequencing technologies (NGS) has resulted in their increased use in research, and in the clinic. However, France and Quebec have not yet implemented nation-wide personalized medicine programs using NGS. To produce policies on the large-scale implementation of NGS, decision makers could benefit from a detailed understanding of how these technologies are currently used, their limitations, and the benefits they could bring to patients.

Objectives: We aimed at answering two research questions: How are patients' NGS data currently managed in healthcare institutions in Quebec and in France? What issues do technology users identify which should be solved in order to implement clinical genomics at the national level?

Method: Through a multiple case study method, we analysed interviews and documentation from four teams that use whole-exome sequencing in hybrid clinical research projects focusing on cancer and rare diseases.

Results: Interviewees detailed numerous challenges linked with managing the complexity of the process of collecting and interpreting data in a relevant manner for patients, and described how obtaining buy-in from multiple stakeholders was necessary.

Conclusion: A strong political will is essential for personalized medicine to be implemented efficiently in France and Quebec.

4.2 Keywords

1. multiple case study
2. next-generation sequencing
3. whole-exome sequencing
4. rare diseases
5. cancer genetics
6. France and Quebec

7. healthcare systems
8. health policy

4.3 Introduction

The decreasing cost of human genome sequencing technologies[284] has resulted in their increased use in research and in the clinic[285]. Indeed, next-generation sequencing (NGS) research results have proven that the correct interpretation of a human genome can improve diagnostic yield for rare diseases[77,97,219,286], and enable a greater efficacy of treatment of certain cancers[109,110,128,287–289]. Recently, the use of these technologies in neonatal care especially in critically ill infants has been launched with great promise and some controversy[62,63,67,68,290]. Today, the sequencing and analysis of a patient's whole exome or whole genome is offered to specific patient groups in a limited number of health institutions around the world, such as in the USA[19,84,291,292] or in the Netherlands[181],or in some other developed countries, in the context of pilot or proof-of-concept projects[110,178,286,293]. In the UK, the Public Health Genomics Foundation has published a number of technical[294–296] and policy reports [283,297] in order to accompany the progressive use of genomic sequencing technologies in « mainstream clinical pathways»[298] in the country, a topic which has generated discussions at the national level [299,300]. The UK's 100.000 genomes project, as well as the United States' precision medicine initiative, renamed the "all-of-us research program", are two examples of large-scale national initiatives in which governments have invested significant resources to build an infrastructure enabling the clinical use of NGS. In this study, we focused on two jurisdictions which have not yet publicly embarked on endeavours of a comparable scale: Quebec and France.

The clinical implementation of NGS poses a number of challenges[1], especially in pediatric populations[2]. Several steps must be performed to enable the data to be transformed, from a raw sequence, to a clinically informative report readable by a physician. However, costs are still high[112], most of the data is still difficult to interpret[301], and bioinformatics tools and pipelines, and data interpretation strategies are only partially standardized at the moment. To be able to produce policy on the large-scale implementation of NGS, decision makers need to understand what this process of standardization entails, and how it currently unfolds within the scientific

and clinical genomics communities. Although numerous teams publish the results they obtain with clinical genomics projects, no case study has been published to our knowledge detailing how French or Quebec teams operate and how those projects function in detail. In this study, we aimed at answering the following research questions: How are patients' NGS data currently managed (produced, accessed, analysed, interpreted and shared) in specific healthcare institutions in Quebec and in France? What issues do technology users identify which should be solved in order to implement clinical genomics at the national level? To answer this question, we used a multiple case study research method.

4.4 Material and Methods

Case studies research is particularly adapted to the study of complex contemporary phenomena[302]. The phenomenon under examination here is the clinical use of NGS. The small number of teams using these technologies in patient care in France and Quebec, as well as the rapid pace at which these technologies are currently developing makes case studies an appropriate methodology to study this phenomenon. We followed the multiple embedded case study methodology as described by Robert Yin[279].

To select cases, we looked for teams which were using NGS to inform patient care, in the context of comparable projects in France and in Quebec. There were two main reasons for us to focus on these two jurisdictions: First, although they have not embarked in large scale precision medicine initiatives, public institutions in both countries have invested significant funding in NGS following a political push for personalized medicine [6,303]. They even recently announced the launch of two large France-Quebec collaborations in this domain[304]. Thus, today, genomics research is performed in both jurisdictions, within a small number of publicly funded healthcare institutions. Contrary to other countries such as the Netherlands or the USA, NGS is usually not considered to be routine care, which makes it more interesting to analyse. Second, both jurisdictions are comparable on many levels. Indeed, although they have significant differences, the French and Quebec public healthcare systems are both universal. In addition, both jurisdictions share the same language, and follow the civil law legal tradition, although Quebec has a hybrid civil and common law system. Based on published literature and information from research collaborators and expert informants, we approached four teams, two in France and two

in Quebec, which perform whole-exome sequencing (WES) on pediatric patients' DNA. All Principal Investigators (PIs) approached agreed for their team to participate in the study. Two teams use WES to improve diagnosis and treatment of pediatric patients and families affected with **rare diseases (RD)**. The two others use it to help pediatric patients with **refractory or relapsing cancers**, to gain understanding of their absence of response to standard treatments, and to find more effective alternative treatments. The processes involved in the clinical use of WES are hereafter referred to as clinical whole exome sequencing (CES). We collected data from interviews, participation to presentations and project documents, and analysed them using the NVivo qualitative data analysis software. Details on information sources, our data analysis methodology and our interview guide are available in additional file.

4.5 Results

4.5.1 Projects motivations and rationale

Since one of our main objective was to understand the way these projects were launched and how they operated, we discussed with interviewees about the projects' main motivations, and the rationale behind their use of WES.

4.5.1.1 Main motivation: helping patients

According to stakeholders interviewed in all four teams, the first and most important motivation behind the design and implementation of CES is to help patients. This is expressed explicitly:

"[…] we decided we wanted to develop this technology at the service of patients" *French Rare Disease PI*

"[…] in the end, we always refer to how we can help the patient" *Quebec Cancer Bioinformatician*

In both RD projects, the most important stated objective was to offer a diagnosis to patients who don't have an "etiological diagnostic" *French RD PI,* often despite having gone through numerous clinical tests – a phenomenon described as a "diagnostic odyssey" *French Rare Disease Clinician.* CES is used to "answer a clinical question" *Quebec Rare Disease Clinician*

about what is causing the symptoms of a specific individual, and obtaining this answer is described as a "success" *Quebec Rare Disease Researcher.*

In addition, stakeholders also described several positive downstream effects of offering a molecular diagnosis to RD patients, such as adapting care, preventing complications, offering new treatments or participation opportunities in clinical trials, and genetic counselling for the family.

At the collective level, the objective is to increase the team's "diagnostic yield", or the overall percentage of patients who obtain a diagnosis after CES testing. In the Quebec team, an additional objective was that of "demonstrating" that CES is possible, and that the team and institution is "capable" of offering this test to patients while respecting clinical standards.

In both cancer projects, CES is described as a "last chance" *French Cancer Bioinformatician* for patients who do not respond to conventional treatments, and who would otherwise be directed towards palliative care. Indeed, 20% of pediatric cancer patients still succumb from the disease. In France, CES is used in new clinical trials, which aim to evaluate the impact of CES on patients' overall survival. Similarly, in Quebec, the CES project is described as a "feasibility study" designed to evaluate the team and institution's capability to offer this alternative within the strict time constraint imposed by the poor survival rate of eligible pediatric cancer patients.

4.5.1.2 Research or clinic?

In this study, we also noticed the complex position of CES projects between research and clinical endeavors. As mentioned above, the ultimate goal of all four projects is to improve patient care. However, when asked directly if the projects were clinical or research projects, stakeholders interviewed provided a range of responses, and sometimes hesitated, demonstrating the complexity of the issue.

When describing the clinical aspects of the projects, stakeholders described their need to comply with formal processes to produce and interpret CES data. Bioinformaticians from all teams stated that they had to use tools that always give the same output from the same input, as opposed to the sorts of tools which can be used in research, where results can vary slightly at each run. Clinicians and PIs described how the interpretation process should be standardized to be able to produce a clinical report, which should include details on each step of the methodology followed.

Stakeholders also described how lengthy and sometimes burdensome the reporting process can be.

Some stakeholders portrayed the research aspects of their projects positively, as a way to be more honest with patients, and avoid therapeutic misconceptions. This also allows teams to systematically collect data on the performance of the technology, which in turn could benefit future patients.

"It is clearly done in a context of clinical research. […] it is important to be able to correctly collect data on which information we have, how we use it, and to evaluate the contribution of what we do specifically." *French Cancer PI*

" we are pursuing the study to be able to analyse more patients because in the end we see the biases… our technical problems, and we get better over time" *Quebec Cancer Clinician*

4.5.1.3 Why the exome?

Even though this question was not specifically asked in the interview guide, all stakeholders described the reasons justifying their choice for this technology, as though they wanted to convince the interviewer that this was a reasonable decision. They all seemed very accustomed to providing these reasons, indicating that they had already presented them in numerous occasions and contexts. Interviewees evoked three categories of reasons:

First, contrary to more focused methods such as gene panels, WES enables the team to examine most genes at once. Performing WES also allows teams to reanalyse "unsolved" patients' data regularly in light of the most recent versions of variant databases and research results. Three of the four teams use "in-silico gene panels analysis" to focus their clinical analysis on a list of genes which are most likely to be clinically relevant for the patient. This list is established by gathering internal and external expertise, and data from international databases and most recent published research results. This enables patients to benefit from this collective knowledge rather than just that of their treating physician, who may order targeted genetic tests based only on his/her knowledge of the disease, which may be partial or outdated. Performing CES also allows teams to publish patients' data into international databases, and in turn participate in increasing the knowledge-base on the genetic background of diseases, which may be useful to other patients.

A second set of reasons put forward was the wealth of published scientific evidence "proving" that this technique is clinically and economically efficient. All teams referred to specific publications[84,87,305–307], work done by institutions or laboratories[a,b,c,d] or projects[e,f,g] as elements of proof that CES, when performed with strict guidelines and quality controls, can be the best option for patients.

Finally, CES was described as "cost-effective". Indeed, performing a series of targeted tests is more expensive than sequencing the whole exome directly. Considering the increasing demand for the test, several PIs explained that it was cheaper to develop the technology internally (at the level of the institution in France, and at the level of the province in Quebec) than to order the test elsewhere (institutions invoicing others for the test in France, or tests being performed out-of-province or in the USA in Quebec). Providing the test as a service to external clients was also described as a source of income for the institutions who offer the test early.

4.5.2 Main challenges in "leveling up"

The fact that the technology is "in transition" was made clear by members of all four teams. They expressed that the context is evolving, and that projects of this kind gradually make their way from the research to the clinical realm. When asked what the current main challenges were, teams provided a wide range of answers (see Table 4.1: Main challenges), some of which were previously identified in the literature, but also others which were either not identified, or not previously described in those terms.

---

[a] Baylor Medical Genetics Laboratories, https://www.bcm.edu/research/medical-genetics-labs/test_detail.cfm?testcode=1500 Accessed 13 April 2018
[b] UCLA Clinical Genomics Center, http://pathology.ucla.edu/genomics Accessed 13 April 2018
[c] Genome Diagnostics Nijmegen, http://www.genomediagnosticsnijmegen.nl/index.php/en/services/exome-sequencing-diagnostics Accessed 13 April 2018
[d] The Terry Fox Research Institute, http://www.tfri.ca/ Accessed 13 April 2018
[e] The Deciphering Developmental Disorders Project, https://www.ddduk.org/ Accessed 13 April 2018
[f] The Care for Rare Project, https://care4rare.ca/ Accessed 13 April 2018
[g] The Kids Cancer Sequencing Program, KiCKS, https://kicsprogram.com/ Accessed 13 April 2018

7) Table 4.1: Main challenges

This table presents interviewees' answers to the following question: "what would you say is the main challenge for clinical exome sequencing to succeed in your country/province?"

		France	Quebec
Cancer	Principal Investigator	Managing the complexity of the data and of cancer	Give targeted molecules identified through WES to patients
	Clinician	Data analysis	Data interpretation
	Bioinformatician	More rapid and efficient data analysis process	Standardized use of analysis software and pipelines
	Head of biochemistry lab	Standard clinical analysis of exome data	
Rare Diseases	Principal Investigator	Education of practitioners to genomics	Gather support from all relevant stakeholders to enable the implementation of the technology in the public healthcare system
	Clinician	Education of biologists and clinicians who participate to data analysis and interpretation	Time and availability of qualified analysis to interpret the flow of data.
	Researcher		Variants clinical interpretation
	Bioinformatician	Challenges linked to the bioinformatician profession, interdisciplinary and at crossroads between biology and computer science	Standardized bioinformatic pipeline for clinical data analysis. More investment in required storage and processing infrastructure

4.5.2.1 Managing the complexity of WES data

WES generates a lot of difficult-to-interpret data for each patient. Indeed, three stakeholders referred to the data stemming out of WES as 'mostly grey' or as situated in a 'grey zone', with an unclear clinical significance. Therefore, many stakeholders expressed challenges linked with the complexity of the CES process, starting from the raw fastQ file generated by the sequencer and ending in an informative clinical report.

- Bioinformatic analysis

When describing the bioinformatic analysis, all teams described how they developed and regularly updated their pipelines. These pipelines are composed of three kinds of steps, each with their associated challenges.

I) Quality control steps, in which specific parameters are chosen to identify the subset of data that reaches the minimum level of quality for a clinical test. The issue is that although there are best practice guidelines, to date there is no formal clinical certification available for genomic tests in France and Quebec, and no collective agreement on what those minimum quality levels are.

II) Software steps, in which the data is gradually transformed from short DNA sequence reads to a list of variants which are carried by the patient. Several software packages that perform the same tasks are available, and they evolve constantly as their developers release new versions of the tools. Again, in the absence of formal standards, choosing which software to include, and when and how to update it, is a challenge.

III) Finally, in the database steps, patients' variants (usually tens of thousands) are filtered through software which predict how they impact the resulting proteins, or through several other lists of variants that have been found in other patients[a,b,c,d,e,a] or in a healthy population[b,c]. Here,

---

[a] ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/ Accessed 13 April 2018
[b] The Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ Accessed 13 April 2018
[c] Orphanet, http://www.orpha.net/consor/cgi-bin/index.php Accessed 13 April 2018
[d] The Cancer Genome Atlas, https://cancergenome.nih.gov/ Accessed 13 April 2018
[e] My Cancer Genome, https://www.mycancergenome.org/ Accessed 13 April 2018

the challenge is to choose which database to use, based on their quality, comprehensiveness, and relevance. Like software tools, databases evolve over time, and not all are available free-of-charge. Another step used by three of the four teams is that of "in-silico panel analysis", in which they focus their analysis on a subset of genes relevant to the clinical question. These lists of genes are established by the teams and are updated regularly based on the most recent published evidence. In the context of cancer, to select actionable variants, they also consider existing drugs targeting the molecular variants, or open clinical trials in which the patient could participate. None of those steps are therefore fixed in time, and stakeholders expressed difficulties associated with the need to constantly monitor the literature and other resources in order to stay up-to-date and offer patients the best possible chance of a clinical answer. They expressed their wish that more resources would be allocated to this at the institutional level.

➢ Clinical interpretation

After these automated or semi-automated steps, which can generate 50 to 80 variants per individual, clinicians and biologists review each "shortlisted" variation *French Rare Disease Clinician*, in order to produce the final CES report. Cases are also discussed in a group with various experts, and the final decision on what to report, reached by consensus, is signed off on by a clinician from the team before it is reported to the ordering clinician and to the patient. The most critical issue mentioned here was the time spent on each patient's data. Indeed, some results are long and complex to interpret, because variants may have been associated with a wide variety of phenotypes, may be of incomplete penetrance, or have an effect that is less well-known. This interpretation process is described as lengthy, complex, and limited by "human capacities" *French Rare Disease Clinician*. Interestingly, several clinicians perceived this step as more critical, more 'empirical' and less standardized than the bioinformatics steps. They described the bioinformatics analysis as a "resolved bottleneck" *Quebec Rare Disease Clinician,* a difficulty that is "manageable" *French Cancer Biochemist*, or a process that is "well-established" *French*

---

[a] FoundationOne, https://www.foundationmedicine.com/genomic-testing/foundation-one Accessed 13 April 2018
[b] The Exome Variant Server, http://evs.gs.washington.edu/EVS/ Accessed 13 April 2018
[c] The Exome Aggregation Consortium (ExAC) http://exac.broadinstitute.org/ Accessed 13 April 2018

Rare Disease Clinician or "well-oiled" *French Cancer Biochemist*. This vision was not shared by the bioinformaticians we interviewed, who also saw their own tasks as 'empirical', and rather described how they felt their most important mission was to deliver a variant list which would be small enough to be "manageable" by clinicians:

"The exome covers too many genes for a human to be able to give a diagnosis on the entirety of the genome. […] And clinicians, cytogeneticists, they focus on twenty, maybe thirty genes. They have trouble focusing on more. I mean, humanly, it's complicated. […] if you give them a list of a hundred mutations… […], clinicians don't want it, they throw it back at your face. He will say, are you crazy, what do you want me to do with this? I want only a list of a few dozens, maximum, of genes involved in cancer, that's it. » *French Cancer Bioinformatician*

Regarding the question as to whether it was desirable and possible to set in place this whole process, by standards, regulations or certification, stakeholders were not all in agreement. For one team's bioinformaticians, this was actually the most important issue:

"for our part, […] it's just… to have first a tested and robust infrastructure, so going from a framework of research, where we have something that works, but that remains slightly blurry, to have something really very… very very structured, very well defined. Ehm... for us that is the biggest step in the short and mid-term… » *Quebec Cancer Bioinformatician*.

Although most agreed that they would benefit from more formal guidelines on how to streamline this process, some expressed that the ideal process would always depend on the specific clinical question asked. Indeed, pipelines and filtering steps are tailored to each project, each patient population, and the overall objective of the CES process. In addition, these regular updates, although burdensome to monitor, were also described as extremely beneficial in improving the efficacy of the CES process, and changing too rapidly to be enshrined in a law:

"The problem is that everything evolves faster than the law can, I think. It evolves very fast, new machines come out every six months. […] so if the law establishes 'you have to use GATK version 3.3.2 for x years' and there is a bug or a functionality that will not evolve because there is a novelty, well you'll be in trouble. That's the problem, it will never evolve as fast." *French Rare Disease Bioinformatician.*

Another issue was that, although efforts are being made in this direction, it may be impossible to generate a consensus around which pipeline teams ought to use, or how to analyze the data.

4.5.2.2 Education

Another identified consequence of the complexity of WES data was the need for more education on clinical genomics. A wide variety of stakeholders were described by team members as needing more training on how to use and interpret genomic data, including biologists, clinicians, geneticists, and bioinformaticians. Interviewees pointed to examples of other teams who had difficulties setting up CES because of a lack of specific training on how to produce, classify and interpret the data. They even mentioned that some groups are not aware of biases in the technology, and are not using it properly, using "wrong filters" *French Cancer Bioinformatician*. In cancer teams specifically, the need for clinicians and others to have a more realistic view of technological limitations of NGS was also highlighted as a way to avoid overselling the technology, and to manage patients' and families' hopes appropriately:

"Then, there is also an emotional dimension behind, where like very often in oncology and in human pathology, in oncology, we sell things like they are a solution, I sometimes end-up in situation where I'm told: "but you have to do the exome, the patient is not well, it's the only way to cure him…" no, it's not the only way to cure him, you mustn't do these things, and all we will generate is information with an insufficient level of proof. And even if we generate with a sufficient level of proof, this doesn't necessarily mean that we have a therapeutic solution to treat him". *French Cancer Biochemist*

Another important element was the critical importance of bioinformaticians, who represent the cornerstone of a successful implementation of CES. Their interdisciplinary training in computer science, statistics and biology is indeed necessary in order to manage the translation of raw sequencing reads into meaningful clinical information. The need to train more bioinformaticians at the national level, and to have more of them involved in teams who want to set up CES, was highlighted repeatedly.

Another category of stakeholders who were portrayed as lacking training in genomics are those in charge of technology assessment at the governmental level. Indeed, their limited knowledge in

this field was seen as a barrier impeding the smooth translation of WES to a clinically approved, governmentally funded test.

4.5.2.3 The need to convince across the board that CES is a good idea.

Another theme that emerged was the need for team members to get buy-in from a complex network of stakeholders. Indeed, establishing and standardizing the process to obtain, analyze and use genomic data in the clinic is complex, and costly in personnel and infrastructure. Therefore, many stakeholders have to be involved, and convinced that the benefits of CES are worth the effort. We have divided these stakeholders into two main categories: practitioners, and governmental stakeholders.

- Clinicians, molecular geneticists and professional societies

First and foremost, interviewees described that clinicians should be convinced that using this test could be beneficial for their patients. When explaining why clinicians are sometimes reluctant to prescribe CES tests, interviewees talked about the "fear" *French Rare Disease PI* of incidental findings (IF) and of uncertainties associated with reporting strategies, the need for an adapted consent form, doubts about the data analysis process, and the need to be convinced that the test is more effective than more classical targeted tests. One solution provided to this issue is to involve the clinicians early-on in the project so that they have a say in how the data is reported to them, and what kind of results they will have to report to their patients.

Secondly, the community of clinical geneticists and professional societies in molecular genetics also have to reach a consensus that WES is more efficient and cost-effective than sequencing a panel of genes. This question was described as "still debated" *French Rare Disease Clinician* and causing "reluctance" *Quebec Rare Disease Researcher* from some, although this resistance was described as being on the decline. The French RD team described how, because of this controversy over the technology, some teams performed WES almost in secret:

"In the clinical framework, I think there are many people who do it but don't dare to say it because […] it's still debated in the geneticists' community - should we or should we not do the exome? Should we study gene panels […] So people are led to do it anyway, and then in a

grey zone diagnosis-research, they don't announce it, it's not clear, and above all they don't talk about it much so it remains unclear." *French Rare Disease Clinician*

Especially in France, the important role of professional societies in generating guidelines on how to design consent forms, on what to include in the report and what to do with IF was described as something that could alleviate controversies around clinical genomics and convince public authorities to invest the necessary resources for responsible use of the technology. Although stakeholders complained about the absence of official French guidelines, they did not portray this as a sufficient reason not to develop the technology. Instead, they followed the guidelines they perceived as most appropriate, such as European recommendations from EuroGenTest[a] for data analysis and interpretation, and the design of CES reports. Existing professional guidelines were also cited by interviewees, such as the ACMG guideline on reporting IFs[163], which all teams have adapted to their local context.

➢ Governmental stakeholders

The other range of stakeholders referred to as critical in implementing clinical genomic testing were governmental institutions involved in healthcare.

In both France and Quebec, the Ministry of Health (MoH) was depicted as the key actor in charge of deciding if and how to implement clinical genomics. In both regions, the process of technology assessment through which that jurisdiction's MoH has already gone to evaluate the clinical validity, clinical utility and economical sustainability of CES was described at length, with insistence on its inefficiencies. One stakeholder expressed the need to "challenge the system" *Quebec Rare Disease PI.* All teams mentioned having participated actively in the process of generating evidence to prove that CES is a valid test, but having failed to 'convince' the government so far. This was done by mounting specific proof-of-concept or medico-economic studies, and by submitting results to the relevant decision-makers. All project leaders described similar frustrations linked to the authorities' inability to recognize the clinical and

[a] The EuroGentest project, http://www.eurogentest.org/index.php?id=160 Accessed 13 April 2018

economic benefits of WES, even though they and other teams around the world had produced an increasing amount of scientific evidence:

"we hit a wall" *Quebec Cancer PI*

"we are fighting since 2012 to make them understand that high throughput is now, not in ten years" *French Rare Disease PI.*

"I think there may also not be enough solid data in the literature, or in what we do in our research to convince them [the government] maybe" *Quebec Cancer Clinicia*n.

They therefore expressed their conviction that in addition to solid scientific and economic evidence, the implementation of WES could not be done without clear political will from the highest levels of government. Indeed, there was consensus that implementing CES entailed a clear commitment of the state to personalized medicine, and could only be done at the national level with a clear country or province-wide organization of services, significant investments in sequencing and data storage infrastructures, and in training of professionals.

"[…] who does what, should there be one, two, three, four platforms? […] Who will capture the sequences, who will return results, depending on the platform how far do we go, should they return raw results, will existing diagnostic labs analyse the data… there is a whole organisation, I would say… biological, to be thought through. With quite notable territorial inequality, I think in terms of training of biologists to interpret the data" *French Rare Disease PI*

Importantly, actors highlighted a need to reach a broad consensus on how to frame the use of WES, namely determining which patients should be offered the test, which doctors should be allowed to order the test, where and how the data should be sequenced, stored and analysed, and finally who should report clinical results and how. The 'finish line' would be for CES to be offered as a standard test for specific patients, with a formal price quotation, reimbursed directly though the public healthcare system.

"*French Rare Disease PI*: And the final success would be that it is paid by the public authorities.

G.B.: The reimbursement.

French Rare Disease PI: Yes, exactly. It would really be the final success. This means that patients with a genetic disease could benefit from this technique in diagnosis, and reimbursed, I mean covered. So covered, how do I say this? Not necessarily 100% from the Social Security, there could be a part covered by private insurance, why not? But that there could be a coverage, really, by the health system."

At the time when interviews were performed, both the French and the Quebec governments were consulting experts on how to implement those tests. We got a sense from all teams that this political will was emerging and that things could move soon in this domain.

4.5.3 What will the future look like?

When asked what the future of clinical genomics would look like in the next five years, stakeholders depicted many changes, illustrating how fast they believed the field is moving. (See Table 4.2: What will change in 5 years?)

8) Table 4.2: What will change in five years?

This table presents interviewees' answers to the following question: "what do you think will change in five years?"

		France	Quebec
Cancer	Principal Investigator	We will know more on the biology of cancers.	Genomics will be integrated in clinical practice, with a hybrid clinical and research mission.
	Clinician	We will have a standardized data analysis process.	WES will be approved for use in the clinic, and more will be understood about the biology of cancer.
	Bioinformatician	Technology will be available across the territory.	WES and transcriptome will be used in the clinic, and all patients will be sequenced.
	Head of biochemistry lab	Technology will be stable and costs will go down	
Rare Diseases	Principal Investigator	WGS will be used instead of WES, and used in rare diseases, cancers and common diseases.	Only one genetic test will be used, WGS, as long as it becomes cheaper than WES and targeted tests.
	Clinician	Genomics will be used for rare diseases, cancers and common diseases.	WES will be a formal clinical test offered with the appropriate resources, and will be applied in more diseases.
	Researcher		WES will be implemented in the clinic, and WGS will be in the process of evaluation for the clinic.
	Bioinformatician	WGS will be used in the clinic.	The process of sequencing and analysis will be standardized throughout the province.

4.5.3.1 Technological developments

First, a number of interviewees talked about technological developments which they are either certain, or hope, will occur within the next five years. Some mentioned the necessary improvement of the "cost and performance" *French Cancer Biochemist* of WES, such as the percentage of exons captured and sequenced at sufficient coverage.

Another important theme was that of the transition from WES to WGS. Indeed, WGS not only enables the analysis of all genes at an equivalent coverage level, but also uncovers large-scale rearrangements, small and large copy-number variants, and intergenic regions. The main difficulty raised about WGS is the cost of storage and computing infrastructures needed to store and process the data. There was a general consensus that in the clinic, the analysis would be focused on the coding regions of the genome first, but that data should be shared and used in research, and should remain accessible for regular clinical reanalysis. In cancer, where researchers and clinicians are confronted with highly complex tumor genomes, stakeholders also described other promising technological developments, like circulating tumor DNA or immunotherapy. Several interviewees therefore described WES as "a first step among others" in clinical genomics:

"The exome is absolutely not an end in itself, but a step, in fact, at the level of genomic technologies, towards tests which will eventually be better but that, in the context… in the present context, is the best we can offer patients within the clinical structure of the hospital" *Quebec Rare Disease Clinician*

4.5.3.2 Transition to clinical standards

Echoing the issues raised in 4.5.2 – Main challenges in "leveling up", most stakeholders also expressed their belief that within five years, WES will probably be a standard clinical test, offered through the public healthcare system to all patients who need it. There will be no "need to do it in the research context" *Quebec Cancer Bioinformatician*, and data interpretation will be rendered easier by advances in research and increased data sharing. Governments will have taken decisions as to which patients to offer the test to, possibly through the setup of "pilot projects" *French Rare Disease PI, Quebec Rare Disease PI*. The production of sequences will be organized throughout the territory, through certified platforms. Analysis pipelines will also have been standardized, and the legislative framework for the storage, sharing and security of patients' WES data, including IFs, will have been established. There will also have been significant progress in the training of practitioners and biologists to use and interpret genomics data to improve patient care. Access to the technology will therefore be organized and democratized.

"I hope I'm not wrong by thinking that in five years, at least the part that we call now 'clinical', this part will really be a clinical test in due form, which means covered by the

government, subject to specific turnaround time but also to resources, to weighted values at the level of the institution, which should in fact help so that, for instance, the time of the analyst would be easier to match the analysis volume." *Quebec Rare Disease Clinician*

In France, however, one PI expressed doubts that the test would be reimbursed by the healthcare system within just five years:

"In terms of reimbursement, etc.… coverage by the social security and all, I think we won't be there at all in five years. No, we have to be lucid… I think it's wishful thinking. But if already we can put in place a system where it stays within nomenclature and that at least some institutions... [hesitation] I think already it would be a huge step. *French Rare Disease PI.*

4.5.3.3 Broaden the access

All teams agreed that cancer and RD were the two domains in which genomic tests would be the most useful in the short term, but some mentioned that this could eventually be useful for patients with common diseases such as diabetes, and for pharmacogenomic testing. In cancer, stakeholders described their hope that all or most patients would be sequenced at diagnosis, and not only when they relapse or after their first unsuccessful treatment, although not all were confident this would be the case within only five years. In France in particular, interviewees described how important it was to resolve the current territorial inequality in access to WES. Currently, a RD or cancer patient may not be offered CES, either because no research team has put it in place so far in the healthcare institution where she is treated, because the institution has not invested in sequencing technologies, or because they don't have qualified personnel in house to interpret the data. He/she may then be forced to travel to another region to access the test, which is a significant issue for patients with low resources or whose condition limits their mobility. It was therefore highlighted that a national organisation for genomic sequencing would allow personalized medicine to be established in France while respecting important French values.

"*French Rare Disease PI:* So that's the ultimate goal, it's to manage that the French organisation would allow for patients who don't have a diagnostic and who are at high suspicion of having a genetic disease to have access to this technology.

GB: Whatever their reference center is… or wherever they are in the territory?

French Rare Disease PI: Well if we want to go back to the 'Franco-French' theme, that's the French idea, it's access to care for all, and at a minimal cost for the patient… so I won't say free because patients are… unfortunately not everything is free, but at the lowest cost for patients. And that is the French vision of health »

4.6 Discussion

4.6.1 Quebec and France

In both regions, the 'political will' which was described by interviewees as indispensable is now present, and both governments have, while data collection for this study was taking place, taken steps to move forward with clinical genomics. In June 2016, the president of the French National Alliance for Life Sciences and Health (Aviesan), published a publicly available report[129] paving the way for medical genomics to be implemented in France by 2025. The two first national sequencing platforms started to be active in the fall of 2017[a]. In 2015, the Quebec Minister of Health sent a call for proposals to all seven supra-regional university hospitals for establishing a clinical genomic platform. It has since received proposals but still not published its final decision, which could mean that although the government acknowledged that CES is needed, this is not 'the political priority' at the moment, or that they are proceeding very cautiously.

4.6.2 Rare diseases and Cancer

Overall, although all four projects are operating at the crossroads between research and clinical practice, cancer projects seem less advanced than RD projects on the translational path. Indeed, RD team members cited numerous publications and collective experiences demonstrating that CES does improve the diagnostic yield of patients with undiagnosed Rare Diseases, and could also contribute to the improvement of treatments in the future. However in cancer, the objective of CES is to contribute to increasing patients' overall survival rate by providing targeted

[a] Announcement of the two first Genome Sequencing plafroms from the France Genomic Medicine 2025 plan, http://solidarites-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/france-genomique Accessed 13 April 2018

treatments. However, team members insisted on the benefits of CES in increasing knowledge and understanding of the disease, and in CES findings providing avenues for future clinical trials, rather than describing CES as currently able to 'save patients'. A number of issues discussed within cancer teams were unique to this context, including, the need to engage with the pharmaceutical industry in order to broaden the scope of trials design and the number of treatments offered to pediatric patients. The time sensitivity and the need to provide CES results as fast as possible also seems much more critical in a context where cancer patients will potentially pass away within a few weeks, rather than in the case of patients who have already been waiting for a diagnosis for several years. Therefore, cancer teams also discussed the need to involve and obtain buy-in from a chain of specialists in the process, from laboratory technicians to surgeons, pathologists, and oncologists, in order to orchestrate the whole CES procedure fast enough to provide potentially actionable results in time. Finally, cancer DNA is much more complex and challenging to extract, isolate and analyse[41] than germline DNA.

In both contexts though, teams described the need to perform the CES test early, as a first-tier test in RD to avoid multiple unsuccessful targeted tests, or at diagnosis instead of after relapse in cancer, in order to have a view of the disease mutational landscape before selecting first-line treatment.

4.6.3 Relevance for policy

By using a case study analysis model, which enables the researcher to build a relationship of trust with stakeholders, and to have a comprehensive view of the way they operate through multiple information sources, we were able to gather information from the ground on elements that are difficult to find otherwise. Indeed, although examples of successful CES implementation projects are becoming more common in the literature, to our knowledge no study has been published so far which identified other 'non-scientific' elements which can impact the success of CES projects. We were indeed able to describe the complexity of logistical, political and interpersonal factors that need to be taken into account, in addition to financial and scientific matters, in order to offer CES to patients at the national level. We strongly believe that results from this and other observational studies could be used to support the development of policies grounded in evidence, which are more likely to be implemented with ease. For instance, we

observed a consensus on the importance of bioinformaticians, and of training more stakeholders in genetics for CES implementation to succeed.

4.6.4 Limitations

Since the start of data collection, major changes have occurred in the legal and regulatory landscape which will impact the clinical use of sequencing in the near-future. For instance, in FR, in addition to the Aviesan report[129], application decrees[a] were published in 2016 on the law on human research (or Jardé law), which will have an impact on the practice of genomics[308,309]. In addition, a large public consultation on the revision of the bioethics laws was launched in March 2018[b], which notably questions citizens on the use of genetic testing and genomic medicine[c]. Another challenging element for data analysis is that teams operated within a complex network of rules and regulations, both at the institutional, regional, national and provincial levels. Relying on actors on the ground is a benefit of the case studies approach, but it can also be a limitation, since their answers may be biased toward advocating for the importance of the projects they developed. Because of the complexity of the method, we were not able to include more than four teams in the study, but other groups may have provided other interesting perspectives on the matter.

---

[a] Official application decree from the Jardé law, Décret no 2016-1537 du 16 novembre 2016 relatif aux recherches impliquant la personne humaine, accessible at http://www.dm-experts.fr/wp-content/uploads/2016/11/2016-11-17_Decret_application_loi_Jarde.pdf . Accessed 13 April 2018

[b] Etats Généraux de la bioéthique, https://etatsgenerauxdelabioethique.fr/ Accessed 13 April 2018

[c] Examens génétiques et médecine génomique, Etats Généraux de la bioéthique, https://etatsgenerauxdelabioethique.fr/project/genetique-et-genomique/presentation/presentation-7 Accessed 13 April 2018

4.7 Conclusions

In this study, we documented the work, challenges, motivations and vision of professionals from Quebec and France who use NGS to inform patient care. Although WES is not a validated clinical test yet, there are teams who do use this technology in the clinic. The CES projects we explored stand at the crossroads of research and the clinic, and display characteristics of both domains, rendering the identification of their appropriate legal and policy framework extremely complex. Implementing CES at the level of these teams required significant financial, scientific, infrastructural, logistical, and inter-personal efforts to streamline the numerous steps required to extract, analyse and interpret CES data. Implementing this technology efficiently at the national level will require similar efforts to be performed at a much greater scale and in a centralized manner, which cannot be done without strong political will at the highest levels of government. Indeed, managing the extreme complexity of CES process and data will require the involvement, buy-in, education and training of a complex network of stakeholders including practitioners and public authorities' representatives. This political will is present in France and also, at some level, in Quebec. Results of this study could be used among other evidence by policy makers in both regions to establish national personalized medicine programs. However, more research is needed on the legal and regulatory frameworks specifically applicable in both regions, taking the specificities of each healthcare system, legal landscape, and population structure into consideration.

4.8 Ethical approval and consent to participate

The procedures followed were assessed by the responsible review committees. This work was approved by the McGill Faculty of Medicine Institutional Review Board (Study number A12-M66-15A), and by Inserm's Institutional Review Board (approval number 15-253). According to the recommendations of these committees, oral consent was obtained from participants in France, and written consent for participants in Quebec.

4.9 Consent for publication

Not applicable

4.10 Availability of data and materials

All documents collected, notes taken during meetings, and interview transcripts are confidential, as they contain information which identifies the participating teams.

4.11 Competing interests

The authors declare no competing interest.

4.12 Funding

This work was supported by:

- Université Paul Sabatier (axes prioritaires stratégiques 2014, GB),
- Exactis Innovation, Network of Centers of Excellence, Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC).
- FRQ-S Chercheur Boursier Junior 2 # 30719 (YJ)
- The Quebec – Clinical Research Organization in Cancer (Q-CROC)
- Mitacs and Globalinks (Globalinks Research Award IT06972, GB)
- Network of Applied Genetic Medicine (Fellowship in Applied Genetics, GB).

4.13 Acknowledgements

We would like to thank all participants from the four teams who contributed with their comments, and insights and for supporting this work. We also thank Didier Dupont for his help

with the setup of NVivo, Frédérique Duplain-Laferrière for her help in providing inter-judge validity, as well as Anne Cambon-Thomsen, Bartha Maria Knoppers, Jacek Majewski, and David Rosenblatt for their comments and support on the design of the study and analysis method. Finally, we also thank Derek So for his invaluable editorial assistance.

CHAPTER 5: AN EXPLORATION OF THE RESEARCH /CLINIC BOUNDARY

Preface

In the research performed in Chapter 4, we realized that the professionals we worked with described their use of WES as pertaining at times, to either, or to both the clinical and the research realms. Indeed, the technologies are still in transition in France and Quebec. However, the context in which NGS is performed has a strong impact on how data collection, storage, analysis and reporting are performed. Indeed, patients and research participants have a different set of rights, associated to different responsibilities and legal duties which are attributed to clinicians and researchers. We therefore decided to explore further the legal context of care and that of research in France and Quebec. By contrasting this legal analysis with the views and experiences described by technology users in our case study, we were able to identify the potential misalignments between the law and scientific practices, created by the "grey zone" in which genomic sequencing is currently performed, between care and research.

Specific authors' contributions (not described in the published manuscript):

- Gabrielle Bertier conducted the legal documents search and recorded all interviews, which were transcribed through a professional service. She logged all collected data into NVivo and conducted the analysis. She conducted the She produced the first draft of the manuscript, and managed the manuscript submission, revisions and contact with the editor.
- Yann Joly proposed the drafting of a second manuscript from the case study data, provided details on the Quebec legal analysis, and revised the manuscript.
- Anne Cambon-Thomsen provided details on the French legal analysis, and revised the manuscript.
- All authors read and approved the final manuscript

The article was accepted for publication in the European Journal of Medical Genetics and is available online at https://doi.org/10.1016/j.ejmg.2018.04.009

IS IT RESEARCH OR IS IT CLINICAL? REVISITING AN OLD FRONTIER THROUGH THE LENS OF NEXT-GENERATION SEQUENCING TECHNOLOGIES.

Gabrielle Bertier[1, 2, *], Anne Cambon-Thomsen[2] and Yann Joly[1]

Affiliations

1 Centre of Genomics and Policy, McGill University Department of Human Genetics, Montreal, Canada

2 Université Toulouse III Paul Sabatier and Inserm UMR 1027, Toulouse, France

*** Corresponding Author**

Addresses

Gabrielle Bertier
Centre of Genomics and Policy, McGill University Department of Human Genetics
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1, Canada
Email: gabrielle.bertier@mail.mcgill.ca Tel: +1 514-398-8957 Fax: +1514-398-4829
Anne Cambon-Thomsen, CNRS Emeritus Research Director
UMR 1027, Inserm, Université Toulouse III - Paul Sabatier
37 allées Jules Guesde F-31000 Toulouse, France
E-mail: anne.cambon-thomsen@univ-tlse3.fr Tel: +33 5 61 14 59 59 Fax: +33 5 61 14 56 23
Yann Joly, Research Director, Centre of Genomics and Policy
Assistant Professor, Department of Human Genetics, McGill University Faculty of Medicine
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1, Canada
Email: yann.joly@mcgill.ca Tel: +1 514-398-7286 Fax: +1 514-398-4829

5.1 Abstract

As next-generation sequencing technologies (NGS) are increasingly used in the clinic, one issue often pointed out in the literature is the fact that their implementation "blurs the line" between research and healthcare. Indeed, NGS data obtained through a research study may have clinical significance, and patients may consent that their data is shared in international databases used in research. This blurred line may increase the risk of therapeutic misconception, or that of over-reporting incidental findings. The law has been used to impose a distinction between the two contexts, but this distinction may not always be as clear in the practice of clinical genomics. To illustrate this, we reviewed the legal frameworks in France and Quebec on the matter, and asked the opinion of stakeholders who use NGS to help cancer and rare disease patients in practice.

We found that while there are clear legal distinctions between research and clinical care, bridges between the two contexts exist, and the law focuses on providing appropriate protections to persons, whether they are patients or research participants. The technology users we interviewed expressed that their use of NGS was designed to help patients, but harbored elements pertaining to research as well as care. We hence saw that NGS technologies are often used with a double objective, both individual care and the creation of collective knowledge. Our results highlight the importance of moving towards research-based care, where clinical information can be progressively enriched with evolutive research results. We also found that there can be a misalignment between scientific experts' views and legal norms of what constitutes research or care, which should be addressed. Our method allowed us to shed light on a grey zone at the edge between research and care, where the full benefits of NGS can be yielded. We believe that this and other evidence from the realities of clinical research practice can be used to design more stable and responsible personalized medicine policies.

5.2 Keywords

Next-Generation Sequencing
Legal Framework
Translational research
France and Quebec
Rare Diseases
Cancer

5.3 Introduction

As next-generation sequencing technologies (NGS) are increasingly used in patient care, one issue often pointed out in the literature is the fact that their implementation "blurs the line" between research and healthcare [208,234,239,247,310–312]. This issue is not new in genetics [313,314], nor is it exclusive to this field, as its importance was first recognised as early as 1979 in the Belmont

report [315]. But the difficulty to distinguish research from care may be exacerbated through the growing use of NGS to help patients that are running out of possible diagnostic (rare diseases) or therapeutic (oncology) options. Indeed, research participants who have had access to whole-genome sequencing (WGS) or whole-exome sequencing (WES) through a research project may consent to be informed of results that are clinically relevant to them or their families. In addition, patients who have benefited from the use of these technologies as part of their care are often asked to consent that their data be anonymized and shared with the research community to advance knowledge on their and other diseases. If the test result is inconclusive, they may also consent that their data be regularly re-analyzed in light of evolving research findings in order to improve their medical prevention and care. Hence, NGS data obtained through a research study may be used for patient care, and a research project can bring new clinical significance to an inconclusive clinical test. This blurred boundary issue stands at the heart of a number of scientific, ethical, legal and administrative considerations. It is indeed linked to the questions of free and informed consent, its content, design and its mode of collection [275,311,316,317]. Since NGS can yield results which are not linked to the specific disease concerned, this also involves the right of patients to know or not to know [239,318,319] about incidental or secondary findings, and particularly the thorny issue of informing children or their parents of incurable or adult-onset conditions [208,247,275,319–321]. It may indeed increase the risk of over-reporting non relevant variants [322], and of therapeutic misconception [208,275,321,323], where patients confuse participation in a research project with undergoing a test required for their medical care. The law has been used to impose a distinction between the contexts of clinical care and research. However, this distinction may not always be as clear in the practice of clinical genomics. To illustrate this, we review the relevant legal provisions of two comparable systems, France and Quebec on the matter, and report views of stakeholders who use NGS to help patients in practice. We chose to study these two jurisdictions because while these technologies are in transition towards meeting clinical standards, they still have an ambiguous regulatory status.

5.4 Methods

First, we conducted an analysis of French and Quebec legal frameworks applicable to the context of medical care and medical research. This analysis aimed at replying to the three following

research questions: What norms are applicable to research with human subjects in France and Quebec? What norms apply to the delivery of care? Is there overlap between the two sets of norms, and if so, how can it be described? Three main databases were used to collect relevant legal documents; namely: Legisquebec[a] for Quebec norms, Legifrance[b] for French norms, and the HumGen database[c] for legal and ethical norms applied to genomics in both jurisdictions. We also consulted the academic literature on the topic. To do so, we used permutations of the terms "research", "clinical use", "clinical", "medical", "healthcare" AND "genomics", "next-generation sequencing", "whole-exome sequencing, "whole-genome sequencing" in three academic databases: Google Scholar[d], Pubmed[e] and Scopus[f]. Keywords were also entered in French, in order to identify publications in the official language shared by the two jurisdictions.

Second, we interrogated technology users on their views and perspectives on the distinction between research and care. Within a larger observational study conducted between 2015 and 2017 on the clinical use of genomics in France and in Quebec, we identified teams who use next-NGS technologies in order to inform patient care. This was done though consultation of the academic literature, and by discussing with genomics experts in France and Quebec. We identified four teams, two in France and two in Quebec, who had implemented the clinical use of these technologies within the context of comparable projects. The small number of teams identified is an indicator of how novel the technologies were in 2015. The technology used in all four projects was WES, therefore we will refer to its clinical use as clinical exome sequencing (CES). Two of these teams use CES to uncover the genetic basis of rare diseases (RD), and two others use it in the context of pediatric oncology. We approached the four team leaders, and all accepted to participate in our study. We obtained ethics approval both in France and Quebec to conduct interviews with professionals from these four teams. In each of the four teams, after obtaining consent[g], we interviewed three types of personnel involved in CES projects: (1)

---

[a] http://legisquebec.gouv.qc.ca/ (accessed 14 April 2018)
[b] https://www.legifrance.gouv.fr/ (accessed 14 April 2018)
[c] http://www.humgen.org/database-laws-policies#box-A-C (accessed 14 April 2018)
[d] https://scholar.google.com/ (accessed 14 April 2018)
[e] https://www.ncbi.nlm.nih.gov/pubmed (accessed 14 April 2018)
[f] https://www.scopus.com/search/form.uri?display=basic (accessed 14 April 2018)
[g] Following recommendations from the ethics boards, oral consent was obtained for participants in France, and written consent in Quebec.

Bioinformaticians in charge of designing and updating the software pipeline used by the team to analyse WES data. (2) Group leaders (or Principal Investigators, PIs) who direct the research teams. (3) Clinicians trained in clinical genetics, and who are in charge of collecting patients' consent for the test, and give results back to patients. For a full description of all interviewees, see **Table 5.1: Study Participants**. We conducted fourteen one-hour semi-directed interviews, which included questions on a range of aspects of participants' use of NGS technologies, including projects organisation, data trajectory, applicable regulatory frameworks, and opinions on the future of these technologies. Interviews were recorded and transcribed verbatim. Interview data was analysed using NVivo. Themes were drawn from interview data using an inductive methodology, and the final thematic tree was validated by two researchers independent from the study. One interview was also co-coded in full to obtain inter-rater validity. The data presented here was extracted from two main sources: First, we present interviewees' response to the two first questions asked, namely "what is your position?" and "in your institution would you say that WES is used in the context of research or in the context of care?". Second, one of the theme extracted from interviews' inductive analysis was that of the research/clinic boundary. Indeed, this theme was discussed by interviewees throughout the interviews. Here, we present a narrative review of how interviewees discussed this theme.

9) Table 5.1: Study participants

Participants' answers to the question: "Could you describe your current position?"

		France	**Quebec**
Cancer	Principal Investigator	Medical doctor and group leader in pediatric clinical research	Senior researcher, professor in the department of pediatrics
	Clinician	Onco-geneticist in charge of recruiting patients to the WES study	Medical resident in pediatric hemato-oncology in charge of recruiting patients to the WES study
	Bioinformatician	Bioinformatician working on institution's bioinformatics platform	Bioinformatician working in the research laboratory
	Head of biochemistry lab	Head of biochemistry lab, responsible for molecular analysis in clinical and research project	**NA**
Rare Diseases	Principal Investigator	Professor in genetics practices clinical genetics	Professor in the pediatric department, research director
	Clinician	University hospital lecturer in clinical genetics participates to clinical and research activities in the team	Medical geneticist, associate professor of medicine
	Clinical Researcher	**NA**	PhD, clinical specialist in medical biology
	Bioinformatician	Research engineer in bioinformatics	Bioinformatician

5.5 Results

5.5.1 The regulatory context

5.5.1.1 France

In France, medical care is governed by the Code of Public Health, which notably describes the rights of healthcare system users, and how they are to be protected[a]. Among those fundamental rights are access to prevention, care needed by one's health state, the continuity of care and the best possible health security[b], as well as the respect of one's dignity[c]. It should be noted that the respect for persons and the protection of human dignity is a provision of the Civil Code, which applies irrespective of the context, whether it's clinical care, research or any other context[d]. Medical interventions required by the health system user include a wide range of acts, from prevention, investigation, treatments, to appropriate care and therapies[e]. Medical professionals' duties are listed in the medical code of deontology which is established and regularly updated by the Order of Medical doctors and transcribed in the Code of Public Health. They are notably required to participate in continuous training about the evolution of knowledge, therapeutic and technical innovations relative to pathologies which can cause a handicap[f].

In the Code of Public Health, research involving human persons is defined as "research organised and practiced on human persons in order to develop biological or medical knowledge"[g]. Different categories of such research are defined according to their impact on research participants. These categories, which were entirely redefined in 2012[h], are as follows: (1) Interventional research which include an intervention on the person that is not justified by

---

[a] Code de la Santé publique Première partie : Protection générale de la santé, Livre Ier : protection des personnes en matière de santé
[b] Code de la Santé publique Article L1110-1
[c] Code de la Santé publique Article L1110-2
[d] « La loi assure la primauté de la personne, interdit toute atteinte à la dignité de celle-ci et garantit le respect de l'être humain dès le commencement de sa vie. » (Article 16 du Code Civil)[e]
[e] Code de la Santé publique Article L1110-5
[f] Code de la Santé publique Article L1110-1-1
[g] Code de la santé publique article L1121-1
[h] Loi n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine

their normal care. (2) Interventional research with only poses minimal risks and constraints to the persons. (3) Non-interventional research which does not pose any risk or constraint. All have to be approved and their protocol overseen by a "persons' protection committee", or Comité de Protection des Personnes. However, it cannot be pursued if the predictable risk to the participant is "out of proportion" compared to the expected benefits to them of the general interest of the research[a]. One can also note that in the French law, research with human persons has to be performed under the direction or supervision of a medical doctor with appropriate experience[b]. As stipulated in the code of deontology, "a medical doctor who participates in biomedical research as an investigator must ensure that the research study's realisation does not alter the trust relationship which exists between him and the patient, nor the continuum of care". In addition, the law specifies that "the interest of research participants always takes precedence over the sole interests of science and society" in accordance with the Helsinki declaration and the Oviedo Convention.

5.5.1.2 Quebec

In QC, according to the Civil Code (art. 11-25), the notion of care is broad, and includes a wide breadth of medical interventions on a human person "including exams, removal of tissue, treatments, or any other intervention of a physical or psychological nature", and this "regardless of their objective", which can be wither "egoistic" or in the direct interest of the individual, or "altruistic", such as in the case of an experimentation [324] . Care is specifically categorized as either required or, not required, by one's state of health. Interventions not required by one's state of health cover a wide range of procedures, including esthetic surgery, voluntary sterilization and participation to research experiments [324]. Research is hence classified as a sub-category of care not required by one's state of health. However, care and research are associated with different legal requirements. Indeed, every physician has a legal duty of care towards his/her patients. The traditional duty to care of the clinician does not impose that he/she should act in function of the cutting edge of scientific research, but rather, that he follows the good standards of practice of his time. In case of legal disagreement about what those standards are, the testimony of expert

[a] Code de la santé publique article L1121-2
[b] Code de la santé publique article L1121-3

witnesses (medical peers) will be required [325]. Additionally, in the Civil Code, care is distinguished from the notion of research which requires a risk benefit analysis and must be approved and monitored by a research ethics committee.[a]

In both countries, hence, while there are clear distinctions between research and clinical care, bridges between the two contexts exist, and the law provides a number of appropriate protections to persons, whether they are healthcare system users or research participants. However, the use of NGS tests in one or the other context will be a source of legal and ethical duties that are quite distinct for researchers and clinicians.

Health Technology Assessment

The scientific and technical distinctions on the definition of clinical relevance, clinical significance, actionability, minimum confidence level and quality controls for a test or exam conducted in a research project or for patient care, make the development of community standards particularly challenging[283,310,311,313,317,319,326]. Indeed, both the clinical laboratory, its staff and the NGS test itself have to be certified and to follow strict minimum standards to be offered as care [325]. Such standards can be defined by institutions such as the International Standards Organization, and can in turn be adopted by national standard organizations both in France and Quebec. Additional certifications, standards or recommendations can be delivered by local health technology assessment authorities such as the high health authority (Haute Autorité de Santé) in France, and the National Institute for Health and Social Service Excellence (Institut National d'Excellence en Santé et Services Sociaux, INESSS) in Quebec. The availability of such certification will also impact tests prescription and reimbursement by the government through the health ministries and national healthcare systems in both jurisdictions.

5.5.2 Stakeholders' perspective

Results from a study carried out by our group on the clinical use of NGS in the clinic in France (FR) and Québec (QC) provide us with a unique glimpse at how different 'scientific' stakeholders directly involved in clinical NGS projects navigate through this maze[a].

[a] Quebec Civil Code Article 20 and 21.

When asked if the WES projects were clinical or research projects, stakeholders interviewed provided a range of responses, demonstrating the complexity of the problem. (see **Table 5.2: Research or Clinic? Stakeholders' responses**).

10) Table 5.2: Research or clinic? Stakeholders' responses

Participants' answers to the question: "Would you say that exome sequencing is performed in your institution in the clinical context or in research?"

Colours legend:

Clinic	In transition, or partly research partly clinic	Research

		France	**Quebec**
Cancer	Principal Investigator	Research	Translational research
	Clinician	Clinical research	Both
	Bioinformatician	Both	Research
	Head of biochemistry lab	Clinical research	**NA**
Rare Diseases	Principal Investigator	Started in research, now transferred to the clinic	Both
	Clinician	Started in research, was transferred to the clinic, and now both applications are running	Clinic
	Clinical Researcher	**NA**	Both
	Bioinformatician	Started in research, was transferred to the clinic	Both

While some interviewees expressed a confident answer to this question, others however were more hesitant, or expressed conflicting views:

"it is something that is done in the clinical context. […]"

---

[a] Bertier G and Joly Y, Clinical exome sequencing in France and Quebec: What are the challenges? What does the future hold? *(Submitted)*

(Same interview) Further in the discussion about test turnaround time: “for now we are working… this side is rather research. You know, we work in a research mode.” *Quebec RD Clinical researcher*

Others clearly expressed the translational aspect of the technology:

“I think it’s part of a project which at the very beginning, historically was research, but that will or that is now transitioning progressively towards the clinic, clearly. Because I think that’s how it happens for … for most tests that are “innovative” or that have to innovate. That means it’s first a proof-of-concept, a proof-of-principle in research, then a transfer towards a routine care… a clinical diagnosis basically. Even if, when I talk to you about research it’s actually clinical people who perform this research, it’s a bit mixed. But for me, it’s something that is translational.” *French RD Bioinformatician.*

In addition to stakeholders’ responses, we have documented the main aspects of the projects which could facilitate a formal distinction between research and clinical contexts in **Table 5.3: Research or clinic? Specific features of the projects**.

11) Table 5.3: Research or clinic? Specific features of the projects

In this table, we describe elements pertaining to the clinical exome sequencing projects described by stakeholders we interviewed, and categorize them based on their research or care classification.

Colours legend:

Clinic | In transition, or partly research partly clinic | Research

	France Rare Diseases	**France Cancer**	**Quebec Rare Diseases**	**Quebec Cancer**
Consent form	Clinic	Research (clinical trial)	Research (platform development)	Research (proof-of concept study)
Funding	Research	Research	Research	Research
Exome sequencing test considered a clinical test by appropriate governmental body	No	No	No	No
Laboratory certified to perform WES	Yes	Yes	Certification in process	Certification in process
Sanger validation of reported variants	Yes	Yes	Yes	Yes
Use of research servers	Yes, but medical data host certification in process	Yes	Yes	Yes
CES report signed by a certified clinician	Yes	Yes	Yes	Yes
CES report added to medical record	Yes	Only if clinical decision based on results	Yes	Only if clinical decision based on results
Data/samples can be used in secondary research	Yes, with patient consent	Yes, with patient consent	Yes, with patient consent	Yes, with patient consent
Team includes researchers and publishes results in scientific publications	Yes	Yes	Yes	Yes

From this table as well, it is clear that the technology is still in transition, and that it combines aspects that pertain to the clinical domain (inclusion of CES results in patients' medical records) and some that suggest that it is used in research endeavors (CES test not formally approved and reimbursed as a clinical test by the government as part of the universal care coverage). This combination of contexts was sometimes portrayed as a sequential order, with clinical use being followed by research use. For instance, in the Quebec project on rare diseases, when a patient has a negative CES result - meaning that no variant was identified which is associated with the patient's presentation with enough confidence to be considered a clinical diagnosis – then the patient switches to 'research exome', meaning that a deeper analysis of the literature will be performed in order to identify more evidence which could lead to a diagnosis. The institution's sequencing platform is also described as one that can be used by clinicians as well as researchers. In the French project on RD as well, upon patients' consent, their variants of uncertain significance can be further investigated by the team in a research endeavor, for instance using matchmaking software to find other patients with the same variants:

"First, we give people back their results, and then we propose to them: would you like us to continue?" The ways in which we can continue are, to be included in a research project, which means continuing to explore individual variations in genes that until then haven't been implicated in human diseases, [which is usually done], in the research laboratory here, or it means sharing their data internationally, or wait to see publications that come out to see if a variation found in the patient can be causal a posteriori. These are the three strategies that are mentioned to families in general." *French RD Clinician.*

One PI also expressed that while the project's main objective is clearly clinical; CES also generates serendipitous research results:

"Obviously, what is super interesting is that it generates so much new data and new knowledge that we have a major implication in research in terms of genes identification, in terms of comprehension of pathophysiology and cellular mechanisms, but our initial aim, I would say the common thread of all this, it is first the patient." *French RD PI.*

5.5.2.1 Clinic: associated to stringent rules

When describing the project as a clinical endeavor, stakeholders mostly emphasized the importance of applying formal, detailed, reproducible processes to produce and interpret CES

data. Bioinformaticians from all teams illustrated that that they had to use tools that always give the same output with the same input, as opposed to tools which can be used in research, whose results can vary slightly at each run.

"Yes, this algorithm is made to be, to be inexact. So you launch it 10 times on the same dataset, you'll see small variations each time. An that, in the clinic, it's just not possible. We just cannot afford this." *French Cancer Clinician*

It is not only a question of standard practice but also of professional obligation, which is tied to a principle of equality between patients:

"In the clinic, we cannot change the parameters, it needs to be something fixed. […] everyone has to be treated in the same way so that there is no bias … this patient has more chance because he was treated with this protocol when this other patient had another one… […] It's in research that we, afterwards, we adapt the parameters depending on the question asked, to improve the results. But in the clinic, we don't have the right to do that. Parameters are fixed, and everyone is analysed in one go. […] In a clinical trial, even when you just change a kit, an exome capture kit or an extraction kit, you have to re-do all validation steps, and re-pass previous patients for which we already had results to make sure we have the same results than before, etc… It's all very strictly framed in the clinic. In research, it's more free." *French Cancer Bioinformatician.*

Clinicians and PIs described how systematic the interpretation process has to be to be able to communicate individual results to patients and use them in the context of clinical care. This includes reporting in a detailed manner which step was followed, perform quality controls at all steps, having at least two experts looking at each patient's data independently, examining each variation systematically, and reporting only those for which there is a high degree of confidence that they are actionable or causal. This process was often described as necessarily long and cumbersome, and, sometimes, as reducing drastically the type of data that can be reported:

"If we want to transform [CES data] into clinical data, it means we have to eliminate 99.9% of the information and hide it, to be in an application standard." *French-Cancer-Biochemist.*

"So generally, when we do a clinical report, we make sure we limit ourselves, we are only interested in a subset of genes. Whereas in research, we focus on all genes. Plus, in the

clinic we are only interested in genes that we call actionable, which means those for which we have a drug that can potentially act on this gene" *French-Cancer-Bioinformatician.*

"It's very narrow what is done in diagnosis, it means we will only look at pathogenic or likely pathogenic variations - not to variants of unknown significance or likely non-pathogenic variants – that are implicated in human disease and that are linked with the patient's presentation. Which means that it's very limited. There are not so many candidate variants in an exome […]. Very often it's zero, often it's one to two, rarely more. So it's very narrow." *French RD Clinician.*

5.5.2.2 Research: an opportunity

When talking about the research nature of the project, stakeholders sometimes portrayed this positively. This was particularly noted in both cancer teams. First, presenting the project as a research endeavour and not a clinical one is a way to avoid over representing the benefits of the project and lower the risk of a therapeutic misconception:

"For me, it's a research project, and it's not standard of care, and I think the patients have to know that this, that it can be different and that some results may be not correct." *French Cancer PI*

This can also allow teams to operate in a framework in which they are formally and systematically collecting data on the efficiency, efficacy and clinical relevance of the technology, and establishing how to best use it for the benefit of patients.

"It is clearly done in a context of clinical research. […] it is a particularly precise choice in [our institution]. […] We have decided to develop [WES] exclusively in the context of biomedical research, which means that patients are included in biomedical research trials which are declared, […] and there is a consent for each patient to inform them that we are in a research context. This research context is important, relative to the normal regulation, and it is important to be able to correctly collect data on which information we have, how we use it, and to evaluate the contribution of what we do specifically." *French Cancer Biochemist*

Research is also described as a context in which there is more freedom than in the clinic, where rules are less stringent, which allows for more flexibility in exploring the data. The fact that patients WES dataset is collected for research purpose also provide teams with the opportunity to use these data to test new software, gradually improve their clinical analysis processes, and

correct biases that they may discover while analyzing the first few patients enrolled in the projects.

« we are pursuing the study to be able to analyse more patients because in the end we see the biases… our technical problems, and we get better overtime » *Quebec Cancer Clinician*

« right now, as I said it is really a research project, and we take advantage, there is a lot of material, there are not many projects at [our institution] in which we have transcriptome and normal and tumor exomes. So we have very rich data. We can test many tools too, because well, there are different publications which arrive regularly, and it allows us to test different ones, see, which are more effective » *Quebec Cancer Bioinformatician*

5.5.2.3 Research: a necessary temporary step

On the other hand, research was also sometimes described rather negatively, as something that cannot be avoided at the moment, because the test is not approved yet as a formal clinical test. In France, the institution which lists all available clinical tests and attributes a price to them (Direction Générale de l'Offre de Soins, DGOS) does not offer a specific quotation for an exome sequencing test, so it cannot be directly funded through the social security system. Since patients never pay for a prescribed test, hospitals can offer it if they manage to pay for it through other means, either through clinical research projects or regional strategic clinical research investments. Similarly, in Quebec, in 2015, exome sequencing was added to the list of tests not to be reimbursed by the public healthcare system. This was done following two reports from the health technology assessment agency INESSS which concluded that WES was not yet ready for clinical implementation in the field of rare diseases [327] or cancer [328].

In countries with universal healthcare systems, technologies that are deemed to be cost-effective and ready for clinical implementation are likely to be refunded by governments. Given that this is not the case yet in Quebec and in France, teams expressed that they are forced to find other ways to fund projects which give patients free access to the technology:

"we are in a research structure which is necessary to bring, if you want, the analysis in a free manner to patients who qualify. In Quebec, we can send tests out of province, analysis which are not available here, but the exome, officially, is excluded from analysis which are admissible to be sent out of Quebec, so we are really, if you want, in a dead end, in a situation in

which we have no choice if we want to go to available analysis, to find a way to fund it in the short term." *Quebec RD Clinician*

"hum…right now… it's both. In fact we don't have the possibility to do it in a clinical framework, we always have to go through… […] through [our project] when we want to do it. That's what's scary, actually, in closing [our study], is that we know that it's beneficial for patients, but we can't... other than in the clinical framework, it's difficult to have access to it." *Quebec Cancer Clinician*

"It is still in the research framework because we are still in development in the sense that, even after almost four years, we do cases, we make reports and all, but it is still not approved by the Ministry" *Quebec RD Clinician*

"In July [2015], there was a publication from the DGOS that came out to define the nomenclature… well the out-of-nomenclature of NGS, and there are three levels … no, two levels... two levels, and it stops- there is no exome level, which means it stops at the panel. There is no level for large panels or exome, there is no proposed quotation" *France Rare Disease PI*

5.6 Discussion

Interviewing stakeholders involved in CES projects allowed us to shed light on the fact that the strict distinction between research and care made by the law is becoming increasingly untenable in certain contexts in clinical NGS. Actors involved in the same project sometimes described it differently, depending on their training or point of view. Research aspects were portrayed either positively, as a way to improve methods and to analyse data in a deeper way than in the clinic. But it was also portrayed rather negatively, as a necessary temporary step before CES is validated as a clinical test and reimbursed by the government. All projects harbored elements that were clearly clinical (such as the care with which results were analysed, or the addition of CES reports to patients' medical file), as well as others which are typical in a research project (research consent forms and use of data in scientific publications). Several elements contribute to this blurry status of CES. First, the key importance of bioinformaticians in processing NGS data and make sense of it. Indeed, they are trained in biology and in informatics but usually not in medicine; and they operate with research methods and tools that evolve rapidly and constantly, which does not fit in the classical model of clinical care. Indeed, operating procedures have to be

formalized, stable and strictly monitored before they are used for patients' care. Second, genomic data is unique to each individual, partly shared with family members, and can inform on present and future health status, which differentiates it from other contexts which may also generate incidental or secondary findings, such as radiology. NGS also generates information of various levels of certainty, and can provide no response, uncertain responses, or a definitive response to a clinical question. Third, the fact that genomics data sharing is always proposed to patients who undergo CES, whether the test is part of their care or whether they are taking part in a research project. Indeed, sharing genomics data is fundamental in increasing our understanding of disease mechanisms [329]. In addition, the relevance of individual patients' CES results for their care can evolve following the development of new scientific knowledge, therefore data sharing can sometimes bring individual benefits to patients if they can be re-identified and have agreed to be re-contacted. In addition, this sharing does not have to be inconsistent with the protection of their privacy if mechanisms such as controlled access are used [330].

In the French law, inspired by the Belmont Report [315], the stated intent of the test is crucial in the distinction between research and clinical care. Indeed, clinical tests are undertaken to benefit one individual patient, as opposed to research interventions which are designed in order to produce generalizable knowledge for the benefit of the community. This distinction between individual and collective anticipated benefits, which originates from principles of protection of human dignity, integrity and autonomy, is not as clear anymore when applying to NGS testing. Indeed, according to the opinion of the experts we interviewed, within their team, the interest of the individual patients and their family is always the primary focus of offering CES, whether it is to resolve a diagnosis odyssey for a patient suffering from a rare disease, or to offer an alternative treatment options to a patient who will otherwise almost certainly succumb to his/her cancer. This was the case whether patients consented to a clinical test, or to participate in a research study or clinical trial. The interest of sharing data and results to promote scientific research and care was also always present and explained to patients, again whether they consented to CES as part of their care or as participants to a research project. More technical aspects were mentioned by interviewees when distinguishing research and clinical spheres, such as the source of funding for the project or the reimbursement of the test, and the relative stiffness of rules (i.e. standards) they have to follow in producing and analysing the data and reporting results. In interpreting these results, we do not suggest that the strict standards applying to the context of care, the

protections of patients, and the guidelines used to clinically interpret NGS data should be abolished and replaced by more flexible research guidelines. Indeed, when used in the context of care, particular attention should be made to the communication of pre-symptomatic diagnosis, and to the release of information in families, which is strictly regulated in the French law[a], as well as in Canadian professional guidelines [165]. Our research however second the suggestion by Stoeklé and colleagues [331] and others, that a cumulation of two objectives, both individual care and the creation of collective knowledge, is not only a reality, but one that is desirable and should be recognised in the practice of clinical genomics. We brought new evidence from technology users of the importance of moving towards research-based care, where clinical information can be progressively enriched with evolutive research results. It also highlights that there can be a misalignment between scientific experts' views and legal norms of what constitutes research or care. This misalignment would need to be addressed to reduce the risk of unnecessary legal and administrative repercussions on experts working in a "grey zone" at the edge of clinical care and research. Our method, through which we analysed the normative frameworks and tested their relevance in the field, allowed us to shed light on this grey zone, where the full benefits of NGS can be yielded. We believe that this and other evidence from the realities of clinical research practice can be used to design more stable and responsible personalized medicine policies.

5.7 Limitations and future steps

Because the results presented here were collected as part of a larger observational study on the clinical use of genome sequencing technologies, our recruitment strategy was not optimized to answer the specific question of the research/clinic boundary. We had a limited number of interviewees, and our results could be biased due to the fact that we interrogated early adopters who have a positive view of the clinical utility of NGS as opposed to targeted genetic testing. In addition to the views of practitioners and technology users, such as those presented in this study,

[a] Arrêté du 8 décembre 2014 définissant les règles de bonnes pratiques relatives à la mise en œuvre de l'information de la parentèle dans le cadre d'un examen des caractéristiques génétiques à finalité médicale.

the views and experiences of citizens and patients, which have been analysed by others [131,332–340], should also be taken into account when considering legal reform. For instance, a national public consultation on the revision of the bioethics laws is now underway in France[a], and is collecting citizen's views notably on the clinical use of genomic sequencing technologies[b]. Such initiatives could also be taken in Quebec. Results from our study, together with other evidence collected from observational studies, or contributions from professional societies and patients' advocates, could be part of the of the body of evidence used by policy-makers when revising laws, and making decisions on tests validation and reimbursement.

5.8 Acknowledgements

We thank Bartha Maria Knoppers, David Rosenblatt and Jacek Majewski for their useful comments on our methods, analysis strategy and manuscript.

5.9 Funding

This work was supported by:

- Université Paul Sabatier (axes prioritaires stratégiques 2014, GB),
- Mitacs and Globalinks (Globalinks Research Award IT06972, GB)
- Network of Applied Genetic Medicine (Fellowship in Applied Genetics, GB)
- Exactis Innovation, Network of Centers of Excellence, Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC)
- The Quebec – Clinical Research Organization in Cancer (Q-CROC)
- FRQ-S Chercheur Boursier Junior 2 # 30719 (YJ)

[a] https://etatsgenerauxdelabioethique.fr/
[b] https://etatsgenerauxdelabioethique.fr/project/genetique-et-genomique/presentation/presentation-7

CHAPTER 6: AN ANALYSIS OF THE REGULATORY LANDSCAPE

Preface

In this Chapter, we aimed to respond to our last research question: Are there gaps in the current regulatory frameworks which should be addressed to enable a responsible and efficient standardized use of NGS in the clinic?

In Chapters 3 and 5, we started to link the results uncovered in Chapters 2 and 4 in the context of regulatory frameworks applicable to clinical genomics. In addition, throughout the thesis, we continuously collected legal and policy documents on genomics, as they were published internationally.

In this final research Chapter, we aimed to provide a thorough narrative description of the complex framework in which clinical genomic programs have to be inserted. This framework is composed of an array of international, national/provincial and local documents of various degrees of normative strength. While we were conducting the research described in Chapter 4, France adopted a national plan for genomic medicine, entitled the Genomic Medicine France 2025, "Plan France Médecine Génomique 2025"[129]. The publication of this National Plan had a major impact on our research and analysis strategy for Chapter 6, since France effectively took a strong position towards a top-down, nation-wide, incremental implementation of genomic medicine with strong objectives aligned for the next 8 years. We therefore chose to describe the plan and the steps leading to its publication in this Chapter. In parallel, during the discussions we had and interviews we conducted in Chapter 4, we were also informally made aware of a plan in development in Quebec towards the implementation of genomic medicine. However, this plan had not been adopted yet. Building on the findings of Chapter 4, in which we showed that a strong political will was essential in order for genomic medicine to be implemented at the national level, we also provide a description of the political contexts in France and Quebec influencing policy making in clinical genomics.

Specific authors' contributions (not described in the manuscript in preparation):

- Gabrielle Bertier conducted the legal documents search and recorded all interviews, which were transcribed through a professional service. She logged all collected data into NVivo and conducted the analysis. She conducted the She produced the first draft of the manuscript, and managed the manuscript submission, revisions and contact with the editor.
- Yann Joly provided details on the Quebec law and public policy analysis, and revised the manuscript.
- Anne Cambon-Thomsen provided details on the French legal analysis, and revised the manuscript.
- All authors read and approved the final manuscript

CLINICAL GENOMICS IN FRANCE AND QUEBEC: WHAT ARE THE LEGAL, POLICY AND POLITICAL GAPS?

Gabrielle Bertier[1,2*], Yann Joly[1]

1. Centre of Genomics and Policy, McGill University Department of Human Genetics.

2. Université Toulouse III Paul Sabatier and Inserm UMR 1027

* Corresponding author

Gabrielle Bertier
Centre of Genomics and Policy, McGill University
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1, Canada
Tel : +1 514-398-8957
gabrielle.bertier@mail.mcgill.ca
-
UMR 1027, Inserm, Univ Toulouse III - Paul Sabatier
37 allées Jules Guesde F-31000 Toulouse, France

Yann Joly, PhD, Ad.E.
Research Director, Centre of Genomics and Policy, Assistant Professor, Department of Human Genetics, McGill University, Faculty of Medicine
740 Dr. Penfield Avenue, Montreal, Quebec H3A 0G1 l Canada
Tel: +1 514-398-7286
yann.joly@mcgill.ca

6.1 Introduction

To have a complete understanding of how next-generation technologies (NGS) such as whole-exome sequencing (WES) and Whole-Genome Sequencing (WGS) could be integrated into healthcare systems in France and Quebec, it is necessary to understand the governance framework in which such technologies would need to be integrated. Indeed, the regulatory framework which currently applies in France and Quebec has been designed to regulate the use of targeted genetic testing in the clinical setting. Because genetic information is unique to an individual and potentially identifying, because it contains information on present and future health status, and because it is shared with family members, it has been afforded special protections, especially in France. Indeed, it is often considered as a particularly sensitive type of personal health data. The introduction of NGS technologies in healthcare implies the production of massive amounts of genetic data, including some that is not related to the patient's phenotype under consideration. WES and WGS results also carry uncertain information, which is difficult to interpret. It is also difficult to de-identify, which can create privacy concerns. Although the use of genetic information in care and research has been heavily debated, no study published to date provides an overview of the regulatory framework applicable in France and Quebec to the specific use of genomic information in those contexts. Hence, our study objective was three-fold: i) to identify all relevant normative, regulatory and policy documents on clinical NGS, ii) to assess if there are gaps in this framework that need to be addressed in for a better integration of NGS in healthcare, and iii) to establish an update of the policy and political context in which NGS-based tests are being introduced in the clinic in France and Quebec, and identify potential policy gaps.

6.2 Methodology

6.2.1 Data collection:

Our objective was to find all potentially relevant normative documents pertaining to the clinical implementation of NGS in France and Quebec. As we aimed to be as comprehensive as possible, we combined several data collection strategies.

First, several relevant documents were identified in through a systematic review we performed in 2015 [1].

Second, our team also performed a case study analysis in which we observed the work of four teams who use clinical NGS in the clinic in France and Quebec [3]. Stakeholders interviewed in this study pointed to a number of relevant scientific publications, normative as well as policy documents which were included in the present analysis. They also described ongoing political or strategic discussions which are not necessarily captured through the literature.

Finally, relevant documents were identified through periodic literature searches performed since September 2014 in scientific databases (pubmed, google scholar, scopus), legal databases (HumGen), on governments or public agencies websites (ministries of health, health technology assessment agencies, funding agencies or research or clinical institutions). Daily notifications alerts were also set up for the following search keys in Pubmed, and publications screened and analysed manually:

- (exome sequencing[Title]) AND clinical[Title])
- ((exome sequencing[title]) OR (exome[title]) OR (whole exome sequencing [title])) AND (clinical application [title/abstract] OR clinical implementation [title/abstract] OR diagnostic yield[title/abstract] OR clinical diagnostic[title/abstract])
- ("exome sequencing"[Title] OR "whole exome sequencing"[Title] OR "exome"[Title]) AND ("rare diseases"[Title/Abstract] OR "rare disease"[Title/Abstract] OR "mendelian disease"[Title/Abstract] OR "mendelian disorder"[Title/Abstract] OR "rare disorder"[Title/Abstract] OR "rare disorders"[Title/Abstract] OR "mendelian disorder"[Title/Abstract] OR "mendelian disorders"[Title/Abstract] OR "genetic disorder"[Title/Abstract] OR "genetic disorders"[Title/Abstract] OR "genetic disease"[Title/Abstract] OR "genetic diseases"[Title/Abstract])
- ("exome sequencing"[Title] OR "whole exome sequencing"[Title] OR "exome"[Title]) AND ("oncology"[Title] OR "pediatric oncology"[Title] OR "pediatric cancer"[Title] OR "driver mutation"[Title] OR "driver mutations"[Title] OR "tumors"[Title] OR "tumor"[Title])
- (case study[Title/Abstract]) AND (genetic'[Title/Abstract] OR genomic'[Title/Abstract] OR genetic testing[Title/Abstract])

6.2.2 Data analysis

Documents collected were categorized according to the following features:
Jurisdiction (international, Europe, Canada, France or Quebec), norm type (law or policy), norm subtype (including but not limited to Report, Statement of principle, policy brief, law, bill, ordinance, code, decree, certification, EU regulation, etc…) and their applicable domain (research, care, or both research and care). Katie Saulnier, Karine Sénécal and Gauthier Chassang, researchers and experts in medical genomics law and policy in were consulted to validate categories and complete/adjust sources selection.
Relevant sections of each document were than extracted in order to analyse their impact on clinical genomics implementation. Sources were then coded according to an abductive method (deductive first, based on the themes identified in previous research[1–4] and inductive second). Once saturation was reached, we grouped the themes in the following theme categories: Consent (content, mode of collection, withdrawal), laboratory processes, privacy protection, genetic discrimination and data sharing, reporting and reimbursement. Results are presented here as a narrative review of existing frameworks and identified policy gaps.

6.3 Results

6.3.1 International normative landmarks in clinical genomics

Since the first development and uses of NGS in research in early 2010, these technologies have evolved rapidly, their throughput increased dramatically and their price dropped exponentially[341]. As a result, they are increasingly integrated to patient care, and even considered routine care in certain clinics. Together with this increased and expanded use, numerous efforts have been made by professional societies to standardize practices. These standardization efforts have revolved around a variety of themes, including but not limited to: tests regulatory oversight and laboratory practices, bioinformatics analysis and variant interpretation, reporting, return of results and handling of secondary or incidental findings.
A majority of these guidelines have stemmed from the United States, where the technology is used to the largest scale in the clinic[1]. American guidelines have generated significant debates in the scientific and clinical genomics communities, however, multiple other countries such as the

UK[296,298] Korea[342], Australia[343] and Holland[344,345] have also produced clinical NGS guidelines. Those will not be discussed here since they don't directly apply to France and Quebec.

6.3.1.1 American guidelines

The American College of Medical Genetics and Genomics (ACMG) has made significant efforts since the development of NGS strategies to establish a curated list of actionable variants of particularly important clinical significance for the population. This effort has lead them to publish the first, and controversial incidental findings reporting guidelines, which stated that any patient who underwent genomic sequencing in the context of care should be communicated their results in case they are found to carry a mutation in a list of 56 specific genes, identified in the guideline [158]. They revised this statement in 2015 to re-establish patients' right not to know of secondary genetic findings [163]. They created a working group which regularly updates this list [346], which currently contains 67 genes[a].

Efforts have also been made to standardize the classification and clinical interpretation of the thousands of variants found in each patient's whole exome or whole genome. The ACMG, together with the American Society of Clinical Oncology, and College of American Pathologists, have joined forces to establish a formal interpretation guideline for germline variants[235], and more recently for somatic variants in the context of cancer[347]. Although extremely recent, these variant classification guidelines have been widely adopted, and adapted locally by laboratories around the world. For instance, the five-tier system, in which variants are classified as pathogenic, likely pathogenic, uncertain significance, likely benign and benign, is now considered a gold-standard in clinical genomics. It is important to note, however, that a recent study found significant discrepancies between laboratories around the US which were tasked with using ACMG guidelines in order to establish the pathogenicity of the same 99 variants[237]. Authors of the study suggest that familiarity with the guideline, and the implication of trained experts in clinical genomics in interpretation are key to ensure high-quality reporting. In addition, collective discussions and consensus building was an effective way to reduce discrepancies and increase interpretation reliability. This suggests that even though genomics data interpretation is becoming more standardized, it will always necessitate the intervention of

[a] https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/

highly trained professionals in a variety of disciplines. In addition to the variant interpretation guidelines, specific guidelines have been published on laboratory standards[272,273] and on the establishment of bioinformatics pipelines[348] for clinical NGS.

6.3.1.2 European guidelines

In Europe, two main guidelines have been published by the European Society of Human Genetics (ESHG). These guidelines have been established with the collaboration of communities of experts involved in the ESHG, and following results from two main research projects funded by the European Commission: TECHGENE[a]. (focused on the development of NGS diagnostic tools for monogenic disorders) and EuroGentest[b] (funded with the objective of harmonizing clinical genetic testing across Europe). It is to be noted the Netherlands and Belgium had a strong leadership in the establishment of these guidelines, notably through the experience of the Nijmegen genome diagnostic laboratory[c] and the Leuven Center for Human Heredity[d].

The fist guideline [268], which was published in 2013, starts by listing a number of challenges linked to the introduction of WGS in the care setting, related to unsolicited findings, population screening, privacy, commercial applications, and the blurring of research and care concept. The ESHG than lists 11 recommendations which are mostly directed to healthcare professionals using the technologies. These recommendations are non-directive, and four out of eleven simply state that guidelines should be established, regarding informed consent, the right not to know and its limitations, on the return of secondary findings in minors and on data re-analysis strategies. However, they do specifically recommend that "in silico" gene panels be used in order to avoid incidental or unsolicited findings, which should be reported by a health-care professional only if they are "indicative of a serious health problem […] that allow for treatment or prevention". The importance of training primary and specialized care practitioners and of informing the public and patients about clinical genomics is also highlighted.

The second guideline [234] , published in 2016, is addressed to clinical laboratories which are in the process of implementing and offering "NGS-based diagnostic tests". It provides detailed

[a] http://www.techgene.org/
[b] http://www.eurogentest.org/index.php?id=160
[c] http://www.genomediagnosticsnijmegen.nl/index.php/en/
[d] https://www.uzleuven.be/nl/centrum-menselijke-erfelijkheid

guidance on required steps to validate a new NGS-based assay, with a strong focus on gene panels. Indeed, tests based on WES or WGS are deemed "acceptable" only insofar as "the analysis is limited to genes that are known to be linked to the disease"[a]. Again, the ESHG's view is that the likelihood of finding secondary or unsolicited findings should be reduced as much as possible, and insist that in case an opt-in or opt-out option is offered to the patient, the laboratories are required to make sure "all the logistics are covered"[b] so that all variants reported are validated and sufficient information is provided to the patient. The decision to offer to report such findings, which should be approved by an ethics committee, can be taken "at the laboratory, institute or national level"[c]. Details on how to establish clinical utility, analytical sensitivity and specificity are provided, together with a number of quality metrics which need to be established and reported at each step of data analysis, from FastQ (raw reads) to BAM (mapped reads) to VCF (variants list) file formats. Sample NGS reports are also provided, to guide laboratories in the design of reports which provide sufficiently nuanced information, while being understandable for ordering clinicians. Interestingly, the guideline also discusses the responsibility of testing laboratories in data re-analysis. It states that although they should not be expected to re-analyse patients' data systematically to report novel findings, they should be responsible for informing referring clinicians if their patient is found to carry a variant that is re-classified, and that this re-classification possibly affects the patient[d]. Finally, recognising that diagnosis yield will be improved internationally through increased data sharing, authors specifically recommend that all aggregated variant frequencies found in healthy individuals should be shared, and that all variants that are found in patients should be submitted to "federated, regional, national and/or international databases"[e]. This could be seen as problematic, as many private laboratories consider this information proprietary, and use it to provide competitive diagnosis yields.

---

[a] Matthijs *et* al, 2016, Statement 34, p.5
[b] Ibid, Statement 11, p.3
[c] Ibid, Statement 10, p.3
[d] Ibid, Statement 30, p.5
[e] Ibid, Statement 37, p.5

6.3.1.3 Canadian guideline

In 2015, the Canadian College of Medical Geneticists (CCMG) published a Position Statement intended to "provide recommendations for Canadian medical geneticists, clinical laboratory geneticists, genetic counsellors and other physicians regarding the use of genome-wide sequencing of germline DNA in the context of clinical genetic diagnosis" [165]. While each province and territory in Canada is responsible for determining clinical test reimbursement, this position statement aimed at providing non-biding guidance to increase consistency in clinical genomic testing offered to patients across Canada. Importantly, it provides a decision chart to guide clinicians in the determination of which patients should be offered NGS testing, as opposed to those who would most likely benefit from targeted testing or other non-genetic tests. According to this chart, untargeted testing should only be offered to patients with either an unspecific clinical presentation, or a phenotype indicating a potentially genetically heterogeneous condition. Prior to the test, written informed content should be collected and patients should be offered the possibility of having their "coded or anonymized"[a] data shared in international databases, or explored in the context of research projects. Although the CCMG is aligned with the ESHG in stating that incidental findings should be avoided as much as possible[b], they also value individual laboratories' autonomy and suggest ways to frame their offer to report such findings. Finally, in addition to laboratory standards which have to be followed to ensure test quality, such as proper accreditation processes, authors also mention that only certified professionals, typically by the CCMG should be authorized to request NGS-based tests and return results to patients[c].

6.3.2 The complexity of normative frameworks applying to clinical genomics in France and Québec.

[a] Boycott *et al*, 2015, recommendation 2.3, p.435
[b] Ibid, recommendation 3, p.435
[c] Ibid, recommendation 4.3, p.436

When establishing the normative framework which applies to the clinical use of NGS, one has to consider a multitude of areas which are potentially impacted. Both the context of care and that of research need to be considered, as well as data protection and privacy regulations which will apply when sharing and accessing genomic data.

6.3.2.1 International declarations and conventions

While already in existence since the early 20th century, fundamental ethical and legal principles for patients and individuals' participation to research have been established at the international level after the second world war, in reaction to the war crimes committed notably in the concentration camps[315,349].

The Nuremberg code, published in 1947, which was established after the Nuremberg trials, lists ten basic principles in conducting human experimentation. It is the first foundational international text establishing the principle of free, informed, and revocable consent in participation to research. The code directly inspired national laws notably in France, such as in the Code of Public health article L.1122-1, which establishes a comprehensive list of all information which should be communicated to a research participant so that their consent is actually informed. [350]. The code however placed the entire responsibility of protecting research participants on individuals performing the research. It also conceived acceptable research endeavors as those which are likely to yield societal benefits while avoiding all unnecessary harm to participants.

In 1964, the Helsinki declaration on Ethical principles for medical research involving human subjects was adopted by the World Medical Association. Inspired by the Nuremberg code, [315] it was constructed as a guide for medical doctors involved in human subject research, and focused on defining their responsibilities towards the protection of research participants. For the first time, it defined a distinction between clinical research (conceived as having direct therapeutic value for the individual participant, who in essence is a patient) and non-therapeutic clinical research. It was subsequently revised 7 times, and two of those revisions are most relevant to genetics research. First, the 1975 revision includes the need for all medical research protocols to undergo ethics review by independent committees. This fundamental requirement has inspired both French, Canadian and Quebec laws [351,352]. Importantly, the 2000 revision of the declaration

specifically added a statement that the declaration does apply to "research on identifiable human material and data". This generated some controversy as some argued that research on non-identifiable data should also be considered research involving human subjects. [353]. Subsequent modifications in 2008 included a more detailed statement on the collection of consent for such research, including an important role for ethics committees:

"For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee."[a]. This revision also included a requirement for all clinical trials to be "registered in a publicly accessible database before recruitment of the first subject"[b]. Finally, the latest revision of the declaration in 2013 included a specification that research conducted on material and data contained in repositories such as biobanks were also considered research on human subjects. This resulted in a new formulation of article 25, now renumbered article 32:

"For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee."

In addition to these foundational documents, which do not contain any specific provision relative to genetics, the United Nations Educational, Scientific and Cultural Organization (UNESCO) notably through it's International Bioethics Committee (IBC), which has gradually taken a prominent role in establishing international bioethics principles, produced three declarations:

- Universal Declaration on the Human Genome and Human Rights, UNESCO, 1997

[a] Declaration of Helsinki, 2008, article 25
[b] Declaration of Helsinki, 2008, article 25, article 19

Following the discovery of DNA, and developments in genetics research, this declaration specifically prohibits genetic discrimination, as early as in its preamble: " Recognizing that research on the human genome and the resulting applications open up vast prospects for progress in improving the health of individuals and of humankind as a whole, but emphasizing that such research should fully respect human dignity, freedom and human rights, as well as the prohibition of all forms of discrimination based on genetic characteristics,". This principle is re-stated in article 6, which states that: "No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity."

Fundamental principles are also asserted specifically in the context of genetic research, such as the need for prior free and informed consent, the right to know and the right not to know, respect for confidentiality of identifiable data, the prohibition of reproductive cloning, the respect for freedom in the conduct of research, the importance of ethics committees and of international co-operation and solidarity.

- International Declaration on Human Genetic Data, UNESCO, 2003

The production of this declaration stemmed from two observations: First, the diverse ways in which genetic data can be used, in research, medicine and as a unique personal identifier for law enforcement purposes. Second, the significant increase of numbers and sizes of biobanks internationally, containing human samples as well as genetic data. The need was therefore recognised for international guidance in order to prevent uses of genetic data that would go against universal human rights and freedoms[a].

Interestingly, the definition of human genetic data provided in the declaration includes only those obtained through germline DNA and leading to "heritable characteristics", therefore excluding somatic mutations[b].

Following the legacy of the declaration on the human genome and human rights, it confers a particular status to genetic information, and therefore has been criticized as promoting undue

[a] http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genetic-data/

[b] UNESCO International Declaration on Human Genetic Data, Article 2 (i).

"genetic exceptionalism"[354]. In terms of consent, article 8 specifies that consent has to be not only prior, free and informed but also "express" in order to collect, store or process samples and data. More practical recommendations are given on how to ensure withdrawal of consent, with the possibility to continue using "irretrievably unlinked" genetic data[a] even after consent is withdrawn. Provisions relative to the availability of genetic counselling[b], as well as the right to access one's own genetic data[c] are also added.

- Universal Declaration on Bioethics and Human Rights (2005).

This declaration was adopted by UNESCO after a push by governments from developing nations to establish an international framework to guide governments in the framing of biomedical research.

Recently, the IBC published a report "updating its reflection on the Human Genome and Human Rights"[355]. Adopted in October 2015, this document is most relevant to clinical genomics, considering that it does provide an analysis of the specific challenges posed by novel technologies such as NGS. The council identified four main ethical issues with the development of personalized medicine (PM). First, the respect for privacy is challenged by NGS. Indeed, access to large datasets and international data sharing is an absolute necessity in order to realise the promises of PM. The overall societal value of improving public health through PM has to be balanced with the individuals' rights to privacy, particularly in a context where cumulated genetic information can be sold by and to private for-profit institutions. Authors of the report also suggest that this generates a need to make consent procedures more rational and more protective, for instance by enforcing a "right of individuals to know at any time what is done with their DNA sample or sequence". Second, the cost of PM interventions still has to be established, and although there is great promise, the report highlights that to date, only « very few gene mutations or variants are really informative ». The third and fourth issues are linked to the difficulties of properly informing patients about the complexities of NGS, which requires training of medical professionals to return understandable and clinically informative results, and

[a] UNESCO International Declaration on Human Genetic Data, Article 9 (b).
[b] Ibid, article 11
[c] Ibid, article 13

the need to protect patients' right not to be informed, or not to be tested. The committee therefore put forward two practical recommendations, which are aimed at regulators and healthcare system administrators, rather than legislators and ethical bodies[a]:

"71. The pharmaco-genomic data associated with a given drug must be incorporated into its prescription label, to help create the optimal possible treatment decision for the patient. Specific regulatory standards, analysis strategies, reference materials and new monitoring tools have to be developed. Regulatory agencies should be entrusted with matching them and checking the validity of various sequencing platforms, so that their reliability can be assured.

72. Reimbursement policies and health care systems need to be redefined to suit the changes that PM can produce. There are many factors that ought to be thought of: the efficacy and the interest of assorted genetic tests among the whole population; cost-effectiveness in relation to benefits; the specificity of payment systems in the context of rare diseases; the way to redefine a 'shared risk' insurance to include the impact of the newer notion of 'individual risk factors'. The specific implications for some ethnic groups should also be considered. Moreover, genetic data should not be misused by employers or insurers."

6.3.2.2 France

- The European context

At the European level, three foundational documents can be cited:

First, the Charter of fundamental rights of the European union, which specifically prohibits eugenic and cloning practices, as well as the importance of respecting free and informed consent in medicine and biology.[b] It also promotes the protection of personal data as a fundamental right, and notably the right of everyone to "access data which has been collected about them".[c] Finally,

[a] Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights, p.18
[b] Charter of fundamental rights of the European Union (2012/C 326/02), article 3
[c] Ibid, article 8

it specifically prohibits discrimination based on genetic features.[a] The charter was integrated to the Lisbon Treaty, which made its provisions biding in all member states. [350]

Second, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, also called the "Oviedo Convention", which was signed in 1997. In chapter IV on the Human genome, Article 12 mentions that predictive genetic tests can only be performed "for health purposes or for scientific research.

linked to health purposes, and subject to appropriate genetic counselling". It is notable that France, which had promulgated its first bioethics laws in 1994, had an important influence in the design of the Convention [350], which explains how similar these provisions are to the ones described in the next section.

Finally, important changes in the European personal data protection landscape have been brought by the new European data protection regulation. Most importantly for genomic medicine, this new regulation with binding force added genetic data as a special category of sensitive data. This regulation now has to be translated in national laws, and the French bill on the protection of personal data[b] has recently been evaluated by the CNIL[c]

➢ The current regulatory landscape in France

In France, since the 1994 bioethics laws, genetic testing, which is actually defined as "examining the genetic characteristics" of an individual, is permitted, but only in two contexts: medicine and research[d]. Any unlawful examination of a person's genetic characteristic is a penal offence punishable by one year of imprisonment and 15.000€ fine[e].

The examination of a person's genetic characteristic is therefore not regulated like any other medical biology test, and is regulated by a specific set of legal provisions and regulations, in

[a] Ibid, article 21
[b] Projet de loi relatif à la protection des données personnelles, accessible at http://www.assemblee-nationale.fr/15/projets/pl0490.asp
[c] Délibération n° 2017-299 du 30 novembre 2017 portant avis sur un projet de loi d'adaptation au droit de l'Union européenne de la loi n°78-17 du janvier 1978 (demande d'avis n°17023753)
[d] Code Civil, article 16-10
[e] Code Pénal, articles 226-25 to 225-28.

terms of intent, lab and personnel certification, consent, information sharing, and authorised data use [350,354]

These provisions have been established in the 1994 bioethics laws, and then evolved marginally, with the 2004 and 2011 revisions of the bioethics laws, finally the 2012 "Jardé law"[a] which application decrees were only published in 2016 and 2017. The provisions listed in these laws framing the use of genetics are reported in the Civil Code, the Penal Code, the Public Health Code and the 78-17 law on informatics, files and freedoms.[b]

The following principles are established in the Civil code, article 16-10 to 16.13:

Written and explicit consent has to be collected from all individuals undergoing genetic testing, after they have been informed of the test's nature and objective. The consent has to mention the objective of the exam, and is retrievable at any moment. Since 2002[c], discrimination on the basis of genetic characteristics is also specifically banned, especially in the context of insurance and work contracts.

Best Practice guidelines regarding test prescription, test implementation, consent, test reports, return of results and medical follow up are indicated in a ministerial order from 2013[d]. These best practice guidelines were established by the Supreme Health Agency (Haute Autorité de Santé, HAS) and the Biomedical Agency (Agence de la Biomédecine, ABM) on the basis of the Organisation for Economic Co-operation and Development (OECD) guidelines for quality assurance in molecular genetic testing and on the Oviedo Convention's Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes. Notably, genetic tests for medical purposes can only be performedwhen their clinical utility is demonstrated, and only within public health institutions, or private laboratories authorised by a Regional Health Agency (Agence Régionale de Santé, ARS) under the control of the Biomedical Agency (Agence de la Biomédecine, ABM). Individual laboratory practitioners

[a] Loi n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine
[b] Loi 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés
[c] Loi n° 2002-303 du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé, articles 4, 98 and 99.
[d] Arrêté du 27 mai 2013 définissant les règles de bonnes pratiques applicables à l'examen des caractéristiques génétiques d'une personne à des fins médicales

also have to be accredited to be able to perform genetic tests, and this accreditation is conditional to the participation to continuous training to update their knowledge in the field.
The French legislator has also given detailed attention to the organisation of familial information "information de la parentèle", and a ministerial order from 2014[a] is dedicated to describing in which cases this information is warranted, and how it should be taking place.

Genetic testing performed in research has to abide by common research with human participants rules (authorisation by an ethics committee (Comité de protection des personnes, CPP), person's consent, favourable benefit-risk balance for participants). In addition, consent from participants has to be written, explicit, informed and retrievable, just like in the medical context[b].
Genetic data are also protected like any other health data, and their processing is strictly forbidden, unless explicit and written consent is given by the individual, and a specific medical or scientific purpose is specified[c].
Two major changes have been brought by the Jardé law.
First, in article 4[d], the possibility for researchers to perform genetic testing based a sample collected for another purpose (such as in the context of care) as long as the person has been informed and is not expressly opposed to such a use. In case the person cannot be found with reasonable efforts, this obligation to inform them can be lifted. However, the provisions of article 4 are not applicable when research results could lift the research participant's anonymity. It hence remains to be seen if ethics committees will consider NGS research to be eligible for article 4's provisions.
Second, in article 1, the categories of research with human persons (which are defined as research endeavours that are organised with and practiced on human beings in order to develop medical or biological knowledge) were profoundly revised.

---

[a] Arrêté du 8 décembre 2014 définissant les règles de bonnes pratiques relatives à la mise en œuvre de l'information de la parentèle dans le cadre d'un examen des caractéristiques génétiques à finalité médicale
[b] Code de la Santé Publique Article L1122-1-1
[c] Loi 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, articles 6 and 7
[d] Loi n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine, article 4

There are now three categories, namely "(1) Interventional research which include an intervention on the person that is not justified by their normal care. (2) Interventional research which only poses minimal risks and constraints to the persons. (3) Non-interventional research which does not pose any risk or constraint."[4]. These new categories, as well as the new rules of attribution of a competent CPP for research projects were also criticized by some, fearing that centralized institutions would be overloaded with data access and project approbation requests, hence paralyzing health research in the country [308,309].

Further harmonization of definitions and uses of research data have been brought after the publication of the European data protection regulation, notably through a ministerial order[a] which modified the Jardé law. Importantly, article 2 of this order introduced the possibility for researchers to continue to use data already obtained when a person uses their right to retract from research. This simple provision will have a major positive impact on genomics research, since the curation of genomics databases is such a crucial issue notably for patients with rare disease.

It is important to understand that non-interventional research which are only based on previously collected personal health data are not covered by these provisions, and are evaluated by a separate mechanism which was created in the 2016 health system modernization law[b]. This process[c] does not require approbation by a CPP, but necessitates the involvement of three institutions; namely the National Commission on Informatics and Freedom (Commission Nationale Informatique et libertés, CNIL) the National Institute of Health Data (Institut national des données de santé, INDS[d], created in April 2017), and the Expert committee for research, studies and evaluations in health (Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé, CEREES). This institutional oversight on research on health data ensures that research projects are respectful of participants' privacy, that the quality of the research protocol is as high as possible, and that the use of personal data is reasonable to

[a] Ordonnance n° 2016-800 du 16 juin 2016 relative aux recherches impliquant la personne humaine

[b] Loi n° 2016-41 du 26 janvier 2016 de modernisation de notre système de santé

[c] https://www.cnil.fr/fr/recherches-dans-le-domaine-de-la-sante-le-nouveau-chapitre-ix-est-applicable

[d] http://www.indsante.fr/

attain the objectives of the project. The health system modernization law[a] also created a National System of Health Data (Système National des Données de Santé, INDS[b]) gathering information from numerous separate health databases, such as the one from the national health security system and that of hospitals. It was created with the intention of facilitating the use of health data in research, in an open science philosophy [356]. In addition, a National Health Identifier (Identifiant National Santé) has been created by decree[c] to uniquely identify each person benefiting from medical care in France.

These initiatives do participate to the overall simplification of access and processing of health data in research, which is a necessity for translational research, genomic medicine and PM to be implemented nation-wide [356]. However, these new and generalized uses of health data should always be conditional on continuous ethical and social oversight, to ensure that human rights are protected for any citizen choosing to share, or not to share their data. [356]

➢ Issues to resolve for the implementation of NGS

Although numerous changes have been brought to the regulatory landscape in the last few months, a number of issues remain unresolved for the implementation of clinical genomics. Some of those issues were highlighted in a January 2018 report by the ABM on the application of the bioethics laws[357]. First, before performing a genetic test, a doctor has to inform patients of the disease's mode of transmission and the potential impact the findings could have on their family before they consent to being tested. However, when performing NGS testing, and even gene panel testing in order to find the genetic background of unexplained phenotypes, no information is available at the time of consent on what can be found. In addition, the legal requirement to inform patients on the specific objective of the test may be difficult to establish when a lot of uncertainty remains regarding potential unsolicited or incidental findings. More generally, as was recognised by the National Ethics Council (Comité Consultatif National

[a] Loi n° 2016-41 du 26 janvier 2016 de modernisation de notre système de santé
[b] https://www.snds.gouv.fr/SNDS/Qu-est-ce-que-le-SNDS
[c] Décret n° 2017-412 du 27 mars 2017 relatif à l'utilisation du numéro d'inscription au répertoire national d'identification des personnes physiques comme identifiant national de santé

d'Éthique, CCNE) in their 2016 advisory report which will be described in the next section[350], the language used in the law has to be changed in order to adapt the consent process and the information of patients on all the different kinds of findings which can be generated by NGS tests. Numerous groups in France are already well advanced in designing comprehensible and comprehensive information sheets on NGS, but these changes, and the specificities of NGS need to be added to the two applicable best practice procedures for genetic testing[a] and familial information[b].

As genomic testing becomes routine, there will be a higher demand for genetic counsellors, and their responsibilities should therefore be increased, so that they are allowed to prescribe genetic testing to family members of patients they have counselled. To date, indeed, only medical genetics professionals or medical doctors are authorized to prescribe genetic tests[c]. The profession of genetic counsellor is regulated in the code of public health, articles Article L1132-1 to Article L1132-7. Genetic counsellors are not medical doctors, and should exercise their counselling and information role under the authority and control of medical doctors who have prescribed a genetic test[d].

Third, the law should specify the status of NGS test reports. If they are added to the patient's electronic health record, they could indeed be shared beyond what is currently authorized by law, which limits the sharing of sensitive information such as results for genetic testing to the prescribing doctor and the testing laboratory. However, an NGS test report can only be used to it's full clinical value if it is interpreted in the context of the patient's medical record, not only by the prescribing doctor at the time of testing, but also by other professionals throughout the patients' care trajectory.

---

[a] Arrêté du 27 mai 2013 définissant les règles de bonnes pratiques applicables à l'examen des caractéristiques génétiques d'une personne à des fins médicales

[b] Arrêté du 8 décembre 2014 définissant les règles de bonnes pratiques relatives à la mise en œuvre de l'information de la parentèle dans le cadre d'un examen des caractéristiques génétiques à finalité médicale

[c] Arrêté du 27 mai 2013 définissant les règles de bonnes pratiques applicables à l'examen des caractéristiques génétiques d'une personne à des fins médicales

[d] Code de la Santé Publique, Article R1132-11

Finally, the ABM highlights two points of incoherence between the bioethics laws and the 2013 law on medical biology[a]. First, according to the ABM, this law requires that laboratories which extract samples should maintain the responsibility for all following steps, including analysis results. This is contradicted by the provisions of the bioethics laws which required that only accredited practitioners and authorized laboratories are allowed to report highly sensitive genetic testing results so prescribing doctors. In addition, the ABM mentions that only medical biologists are allowed to sign biomedical test reports since the 2013 law, however specific expertise is scarce in interpreting clinical genomics data, and scientists, or competent medical doctors should be allowed to sign reports if NGS tests are generalized.

6.3.2.3 Quebec

In Quebec, there are no laws that specifically address genetic testing or genetic data. However, rights and protections afforded to citizens in the context of care and research are described in the Quebec's Charter of Fundamental Rights and Freedoms, as well as in the Civil Code.
More specifically, article 3 of the Civil code of Quebec establishes that:
"Every person is the holder of personality rights, such as the right to life, the right to the inviolability and integrity of his person, and the right to the respect of his name, reputation and privacy. These rights are inalienable."
Consent is a fundamental pre-requisite to undergoing care[b], and participating to research, and the way this consent can be expressed and collected in different context is a significant focus of the Civil Code, which contains no less than 251 instances of the term. Care is divided into those interventions that are required or not required by the person's state of health.

In terms of data protection, there is no mention of any particular provision specific to genetic data, however because it can be identifying, genomic data can be considered "personal information" and therefore regulated by the Act respecting access to documents held by public bodies and the protection of personal information[c] and the Act respecting the protection of

[a] LOI n° 2013-442 du 30 mai 2013 portant réforme de la biologie médicale
[b] Civil Code of Quebec, article 11
[c] Chapter A-2.1

personal information in the private sector[a]. Indeed, article 54 of the former act, and article 2 of the latter act defines personal information as "any information which relates to a natural person and allows that person to be identified." Therefore, one can safely interpret that any non-anonymous use of genetic data has to be consented to by the person[324], as provided by Article 6 of the act. Privacy protections are also established in the charter of Human Rights and Freedoms, article 5: "Every person has a right to respect for his private life." and article 9 "Every person has a right to non-disclosure of confidential information". Article 9 also includes provisions on professional secrecy.

The Quebec Civil Code article 35 also states that "Every person has a right to the respect of his reputation and privacy. The privacy of a person may not be invaded without the consent of the person or without the invasion being authorized by law."

According to article 24 of the civil code, consent is required in writing only in the context of care not required by a person's state of health, for the alienation of a part of a person's body, or to participate to research that could interfere with the integrity of the person. However, ethics committees are charged with deciding what is the most appropriate process to collect consent in such research, and consent "may be withdrawn at any time, even verbally."[b]

It is to be noted that non-discrimination principles are established in the Quebec charter of human rights and freedoms, articles 10 to 20, especially in employment and insurance, but the charter does not specifically mention genetic characteristics as an unauthorised ground for discrimination. In addition, the use of health information is acceptable in insurance contracts as long as it is used as a "risk determination factor"[c]. It could then be interpreted that a genetic predisposition is by essence a risk determination factor, which can be used in the determination of an insurance contract. However, in March of 2017, bill S-201 was adopted and the federal Genetic Non-Discrimination Act[d] was given royal assent May 4th. This Federal Act criminalizes the request for persons to undergo genetic testing, or to disclose their genetic testing results in order to conclude contracts for with goods or services, or in the context of a contractual

[a] Chapter P-39.1
[b] Civil Code of Quebec, article 24.
[c] Quebec Charter for human rights and freedoms, article 20.1
[d] S.C. 2017, c. 3

agreement with them. The act amended the Canada Labour Code[a] and the Canadian Human Rights Act[b]. This last amendment effectively includes genetic characteristics as a stated prohibited ground of discrimination in the Human Rights Act. However, the constitutionality of the act has been questioned and is now under consideration by the Quebec Court of Appeal. The adoption of the act was the result of numerous years of debate, and is seen by many patient advocates, researchers and healthcare providers as a significant progress in ensuring that Canadians are not negatively affected in their access to care, or in their participation to research because of a fear for genetic discrimination.

In terms of policy, the fundamental document regulating research ethics is the Tri-council policy statement on the Ethical Conduct for Research Involving Humans, which stems from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada. (TCPS2). This document is not legally binding in Quebec, but it is the gold standard that is followed by all ethics committees that oversee research practices in Quebec and all provinces and territories in Canada. The role of such committees is put forward so prominently in the Quebec Civil Code that the TCPS2's status is firmer than that of a simple policy guideline.

The TCPS2, which was revised in 2014, provides a clear and universal guidance on Canadian researchers can ensure compliance with main ethical principles, such as the consent process, fairness and equity in research participation, the protection of participants' privacy and confidentiality, and how to avoid conflict of interests. It also contains more specific chapters dedicated to research types, such as chapter 11 on clinical trials, and chapter 13 on human genetic research. In this chapter, details are provided on the requirements for researchers to establish a clear plan "for managing information revealed through genetic research". Researchers are free to decide whether to share individual findings with participants, or to exclusively

[a] Canada Labour Code, DIVISION XV.3, articles 2-6. Employees can refuse to undergo or disclose the result of a genetic test, this refusal cannot be used as a basis to undergo any kind of disciplinary action on employees, and written consent shall be obtained before results are collected or used by an employer, or disclosed to an employer.

[b] Canadian Human Rights Act articles 2 and 3(3).

disclose "non-identifiable research results". In case researchers do decide to return individual results to participants, measures should be taken so that they can:

"(a) make informed choices about whether they wish to receive information about themselves; and

(b) express preferences about whether information will be shared with biological relatives, or others with whom the participants have a family, community or group relationship."

The "right not to know" is specifically mentioned, and researchers are required to detail how the return of result will be organized, whether it is directly or through a healthcare provider, as long as appropriate genetic counselling options are given to patients when necessary. Also, the guideline mentions that "Participants in genetic research shall have an opportunity to express their preferences about the sharing of information with relatives or others. These preferences may be subject to overriding considerations that may warrant disclosure of information to relatives in exceptional circumstances (e.g., if genetic research reveals information about a serious or life-threatening condition that can be prevented or treated through intervention)". The provisions of the TCPS2 are therefore quite non-directive, and provide research participants with the opportunity to make informed and autonomous choices as to how their participation may impact their care, and that of their family members.

In analysing the Quebec legal framework, we did not see any major impediment to the use of NGS in care. A topic that is however debated in the literature and could be determined by courts, is how the use of these new technologies may affect medical doctors and other stakeholders' responsibilities towards patients and research participants. There is no case law to date regarding litigation on the use of NGS, but authors have suggested that questions may arise regarding the evolving responsibilities of medical doctors regarding the return of clinically relevant research results, the complex interpretation of genomics data, and the need for a collective analysis process, [157,209,358,359]. In addition, recent controversies on the commercial use of health data[ab] may

[a] http://www.lapresse.ca/actualites/sante/201803/06/01-5156223-qui-surveille-lacces-aux-dossiers-medicaux-electroniques-.php

[b] http://www.lapresse.ca/actualites/sante/201803/02/01-5155859-dossiers-medicaux-a-vendre.php

make the public more critical of the kinds of protections they are really afforded, and may complexify the addition of genomics data in medical records.

6.3.3 Implementation of clinical genomics: a portrait of the organizational and political contexts in France and Quebec

6.3.3.1 France

- Rare diseases and Cancer: pioneers in genomic medicine?

In France, many cancer and rare disease patients already have access to genetic testing. Indeed, multiple research and clinical institutions are tasked with realising the ambitious objectives set out in multi-annual national plans that have recognised the key importance of genetics in these two areas for several years. National Plans represent governmental priorities, and represent a strong governmental commitment. Their governance is organized by the responsible ministries, and annual reports are submitted to the President for review. In addition, part of the budget to execute the plans' measures is voted within the annual national budget that is approved by the parliament. Although the plans have not direct normative value, certain emblematic measures set forth in the plans can be included in the law. For instance, the recognition of the "right to being forgotten" (droit à l'oubli), an objective in the 3rd Cancer Plan[a] was integrated in the 2016 health law[b]. Numerous cancer patients now have the right not to mention to their insurance or bank that they have had the disease, five to ten years after the end of the treatment protocol[360,361]. Both cancer and rare disease plans are based on a dense and highly organised network of care institutions which ensure that patients have access to the best care possible, regardless of where they are located on the territory. One difficulty in analysing all available data, is that the term NGS is used to describe the sequencing of small gene panels (often called targeted NGS,

[a] Plan Cancer 2014-2019, Action 9.13
[b] Loi n° 2016-41 du 26 janvier 2016 de modernisation de notre système de santé, Article 190.

sometimes NGS for short) as well as WES or WGS. Neither WES or WGS are listed in the National Biology Table[a], which lists approved and priced acts to be reimbursed by the social security system.

The second rare disease plan, which was originally planned to end in 2014, was extended until 2016, and the third rare disease plan is currently still in construction. Still, in late 2017, 387 reference centers have obtained the 2017-2022 rare disease reference center label (against 113 in the previous label period), with 1841 competence centers (previously 500) throughout the territory, and have been allocated 45 million euros to perform their activities. These centers (the full list is available on the health ministry's website[b]) gather multidisciplinary and multi-professional teams with a specific expertise in one of the 23 rare disease areas[c]. A network of national experts is active in each of these areas, which notably include anomalies of development and intellectual defects (AnDDi-Rare), mitochondrial defects, cardiovascular diseases or diseases affecting the central nervous system (Brain team)[d].

In the 2017 rare disease centers activity report [362], it is mentioned that more than one *filière* have engaged in activities aimed at collecting evidence and creating recommendations on the use of NGS. For instance, the AnDDI-Rare network has been heavily engaged in the development of research evidence through clinical demonstration projects, and has organised several expert focus groups on NGS. Notably in collaboration with the National association of Molecular Genetics Practitioners (Association Nationale des Praticiens en Génétique Moléculaire, ANPGM), which has set up an NGS network, they have published recommendations regarding data analysis and reporting of NGS tests, which are available on the AnDDI-Rares website[e]. However, the vast majority of patients who have had access to sequencing to date have done so as research participants, and the 2017 rare diseases activity report concludes that access to NGS-based

[a] http://www.codage.ext.cnamts.fr/codif/nabm//telecharge/index_tele.php?p_site=AMELI
[b] http://solidarites-sante.gouv.fr/fichiers/bo/2017/17-11/ste_20170011_0000_0109.pdf
[c] These areas are called "filières maladies rares" in French
[d] http://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/maladies-rares/article/l-offre-de-soins#
[e] Details on the organisation of the rare disease network in France, are available on the page from the Ministry of Health and Solidarities http://www.anddi-rares.org/nos-actions/soigner/guides-procedures-protocoles.html

diagnostic will be coordinated through the France Medical Genomics 2025 Plan (Plan France Médecine Génomique 2025, PFMG2025.

In France, the biomedicine agency (Agence de la Biomédecine, ABM) is the institution that centralizes all molecular genetic testing services throughout the territory. In it's latest report published in 2016, gathering data from 185 molecular genetics laboratories in France, neither gene panels nor NGS techniques are identified as a specific category of molecular genetic analysis. However, one figure in the report (Figure POSTNATAL5) represents the number of tests approved, classified by the number of kilobase covered by the tests. The categories themselves are representatives of how the report is still geared towards targeted analysis, since the highest category, in which 2,609 tests have been performed, is "above 500kb" (a WES test would cover a minimum of 50.000 kb). Indeed, according to the Orphanet website, only three laboratories are accredited to perform clinical whole-exome sequencing in France[a]. The AnDDI-Rare group has also established a dynamic map of France, highlighting where WES is available to rare-disease patients, which so far indicates that only two Hospitals offer it routinely to all patients (Namely Dijon and Pitié Saplétrière in Paris)[b]. France is highly active in rare disease clinical genomics, but mostly through research and demonstration projects, as exemplified by one of the latest call for projects from the Rare Disease Foundation (Fondation Maladies Rares, FMR) entirely focused on genomics[c].

The situation is similar in the context of Cancer. Under the leadership of the National Cancer Institute (Institut National du Cancer, INCa) and the General Directorate for Care Provision (Direction Générale de l'Offre de Soins, DGOS), a network of 28 molecular genetic platforms have performed 35.000 targeted NGS tests (gene panel) in 2016, and a total of 83.000 patients have had their tumor tested for a potential match to access one of 30 available targeted

[a] http://www.orpha.net/consor/cgi-bin/ClinicalLabs_Diagnostictest.php?lng=EN. Note that the methodology used to establish this list of laboratories is not specified in the website, which could mean that some are missed.

[b] http://www.anddi-rares.org/nos-actions/soigner/optimisation-du-developpement-du-sequencage-nouvelle-generation-ngs.html

[c] http://fondation-maladiesrares.org/wp-content/uploads/2018/01/2018-1-FondationMR_HTS-RD.pdf

therapies[a]. More specifically, the latest Cancer Plan (2014-2019) planned for the sequencing of 3.000 patients' whole genome by 2015, a number which was supposed to rise to 10 to 15.000 by 2017, and 50.000 by 2019. As of 2017, none have been effectively realised, although several clinical trials are currently running which do include NGS strategies[363]. The Cancer plan also aimed for the creation of a national platform dedicated to genomics and cancer data analysis. Again, many patients have had access to the technologies in the context of research projects, through mechanisms such as teaching, research, reference and innovation missions (Missions d'Enseignement, de Recherche, de Référence et d'Innovation, MERRI) funded by the MoH. The INCa in it's latest report does mention that it is partnering actively with the PFMG2025 to offer NGS to patients, but still, no patient has yet had access to NGS testing of their tumor as part of their routine cancer care to date in France[363].

The fact that efforts are made in the context of research before NGS is implemented in the clinic is positive, in the sense that numerous centers have managed to purchase equipment and have been testing the methods for years, rendering the clinical implementation more rational. However, this highly competitive research environment has also been a source of duplication, and of a lack of cross-center coordination, which results in a situation of de-facto territorial NGS access inequality for patients throughout the territory [364]. There is high hope however that the PFMG2025 will coordinate strategies and rationalize access at the national level in the coming years.

➢ Policy reports leading the way to France Genomic Medicine 2025 Plan

In January 2014, the Parliamentary Office for Scientific and Technological Choices (Office Parlementaire des Choix Scientifiques et Technologiques, OPESCT) published a report entitled: Progress in genetics; towards precision medicine? Scientific, technological, social and ethical challenges of PM [365]. After consulting with numerous experts and visiting the main sites in France which were already offering genomic testing, they concluded this report with a list of 44

[a] http://www.e-cancer.fr/Professionnels-de-sante/Les-therapies-ciblees/Les-plateformes-de-genetique-moleculaire-des-cancers/Missions-et-localisation-des-plateformes

specific recommendations divided in seven sections, in order "prepare for the paradigm shift induced by PM in how we approach disease and treatment". The recommendations focus on maintaining support for clinical research and development, better articulating the roles of each actor in the health care pathway, reforming the training of care professionals, in informatics notably, and ensuring equal access to all citizens to novel therapies. They also recommend to better inform citizens about PM, its opportunities and challenges, and to continue to provide strong protections for personal health data. It should be noted that some measures recommended have already been put in place, such as a general website to inform the public on medical genetics, hosted by the ABM[a]. The website even includes a description of NGS technologies with an explanatory video on the benefits brought by NGS in rare disease diagnostic[b]. Information sheets for patients notably in rare diseases have also been developed by AnDDi-Rares[c], and by TRANSLAD[d], a university-hospital federation (Fédération Hospitalo-Universitaire, FHU)[e] labelled initiative dedicated to developing and harmonizing care, research and teaching in rare diseases with anomalies of development.

In January 2016, the National Ethics Council (Comité Consultatif National d'Éthique, CCNE) published it's 124th advisory report [350] entitled: Ethical reflection on the evolution of genetic tests linked with high throughput human DNA sequencing. This report aimed at proposing a « anticipatory reflection on the conditions allowing for a regulatory system to be efficient and respectful of persons ». After describing the current uses of genomic sequencing techniques, both within and outside of the medical context, the CCNE warns about the risks of commodification of personal data posed by huge private investments in this new field which could represent a lucrative market, both in terms of selling machines and reagents (especially in oncology and prenatal testing), and personal data. They mention that while that none of the questions posed by genomic sequencing are properly new, the radical change in scale that they bring warrants an anticipatory ethical reflection.

---

[a] https://www.agence-biomedecine.fr/Site-pour-le-grand-public#genetique-medicale
[b] https://www.genetique-medicale.fr/en-videos/article/sequencage-haut-debit
[c] http://www.anddi-rares.org/assets/files/plaquette-sequencage_haut_debit_exome.pdf
[d] http://www.translad.org/assets/files/sequencage-haut-debit-exome.pdf
[e] http://www.translad.org/presentation.html

For instance, the Committee also highlights the importance of differentiating the kind of information provided by NGS technologies (solicited or incidental, clinically relevant or not, actionable or not, of certain or uncertain significance) and of offering patients the opportunity to consent to obtain or not be informed about all these kinds of data/information. They also underline the importance of establishing a standardized protocol to follow in case Incidental Findings (IFs) are uncovered, and discuss this with each patient through the consent process. Principles of necessity and proportionality should be respected in offering patients each kind of information. The report mentions that NGS technologies bring about uncertainty at two levels for the medical doctor: on the pertinence of actually ordering a test, and in the clinical relevance of the test report, and the impact it should have on care. The Committee recommends that the clinical relevance and security of applications of genomics be ensured through strict control mechanisms, while it should also always be based on the evolution of scientific evidence, following the model of evidence-based medicine. This however generated a difficulty, in that medical doctors must also be kept aware of the constant evolution of knowledge to be able to interpret genomic data. The report therefore highlights the importance of training medical doctors to better understand the uncertainties brought about by genomic data and the necessity of protecting patients' privacy.

On the topic of privacy, the CCNE describes the need to abide by existing privacy regulations, and consider genetic data like any other sensitive health data. It includes notably the need to define ahead of time the acceptable use of data, and exclude unacceptable or unplanned uses of these collected data, which should be described in the informed consent documentation. However, the CCNE does recognise that the process of free and informed consent should be revised in order to take into account the high probability of having unexpected findings, and the evolutive nature of the clinical interpretation process. No concrete recommendation is given on how to achieve such a revision, except that of organising a democratic debate involving all relevant stakeholders, which they recognise will take time.

They also recognise that individuals can willingly consent to share their data following the "auto-determination principle" for the "common good", which includes research and public health. But interestingly, they assert that this consent should not be incompatible with the respect for their privacy, and should not give the right to third parties to violate their privacy rights. In addition, individuals should always have the right to retrieve their consent to share their data, which the

CCNE recognises is, with current regulations, unpractical, or at least suboptimal. Finally, the CCNE warns against an over-emphasis on genetics as opposed to social determinants of health, and the resulting risk for genetic discrimination. Finally, the committee raises the question of the necessary evolution from the « blockbuster » drug model, to more targeted approaches, to which the pharmaceutical industry is adapting but which generates very high costs.
Overall, the report does have a rather cautionary tone, and even criticizes certain international reports such as the one published by the UK's Human Genetics Commission in 2011 entitled Increasing options, informing choice: A report on preconception genetic testing and screening" [366], as reflecting a "fascination" for technical and scientific progress in modern human genomics. The CCNE's report does reassert important principles of respect for human dignity, privacy and solidarity in the healthcare system, but lacks concrete recommendations as to how to ensure their respect while embracing the promises of clinical genomics.

In February 2016, the National Medicine Agency and Technologies Academy published a report entitled: Report and recommendations on the implementation of next-generation sequencing techniques in France [367]. This joint report starts by asserting that France is advanced in molecular genetics, both in research and in the clinic, citing again the example of the National Cancer Institute's network of 28 molecular genetics platforms allowing any patient with one of the most common cancer type (colorectal, lung, leukemia, breast) to have his tumor sequenced by targeted NGS and to be potentially provided access to targeted therapies. However, they highlight France's delay in implementing genome-wide NGS in the clinic, and the absence of "high-throughput national structures with the capacity to perform hundreds of thousands of analyses per year" such as those found in the US, China or the UK. In a specific manner, they list organisational, regulatory, technological, economic, educational and ethical issues that need to be taken into account in the creation of such a centralised national structure. At the time the report was published, the PFMG2025 was already in the works, and the concept of a centralized data center with 10 to 15 high throughput sequencing centers throughout the territory, proposed by the plan, is supported by authors. Considering the ambitious scale of the initiative though, authors do suggest that a pilot project be launched to test the viability of such a structure.

In terms of technological developments, authors warn against a potential long-term monopoly of Illumina on sequencing machines, and urge France to support European and national innovations in terms of samples preparation, sequencing techniques and data processing and analysis software. The report highlights the importance of designing a more flexible legal framework to enable a responsible cross examination of health data and genomic data collected in research. They also point out that the clinical utility of NGS tests should be established before they enter the social security reimbursement realm, and that this is not yet the case. Indeed, authors mention that "the decision taken this summer by the Ministry of Health to leave under the authority of the social security only sequencing of less than 500 kb, exclude (voluntarily) whole exome and whole genome sequencing". However, the origin of this information is difficult to verify. Although PM though NGS necessitates a significant investment, authors mention that economic benefits could be generated, especially if France develops its expertise in human and non-human genomics in partnership with private and industrial partners. The critical need to train more bioinformaticians, and to create specific interdisciplinary training in PM is highlighted by authors. Ethical considerations are also listed, such as the challenges raised by secondary and incidental findings, and those associated with direct-to consumer genetic testing. Finally, authors conclude with 6 specific recommendations, namely to:

1. Create a collaborative pilot project with the capacity to sequence, store and interpret 40k whole genomes per year.
2. Design incentives for the creation of a French or European competitor for Illumina to try and end their monopoly.
3. Develop novel sample preparation and data analysis methods through collaborations between geneticists and industrial partners.
4. Adapt the law so that genomics research projects may be approved without being based on a pre-determined patho-physiological hypothesis.
5. Facilitate the cross-analysis of genomic and clinical data while respecting patients' privacy.
6. Plan for the creation of 10 to 15 sequencing centers throughout the territory and link the network to one central national data management center.

➢ The France Genomic Medicine 2025 Plan (PFMG2025)

In April 2015, the French prime minister at the time, Manuel Valls, mandated the National Agency for Life and health sciences (Agence Nationale pour les sciences de la vie et la santé, Aviesan) to produce a report establishing a 10 years plan towards the realisation of genomic medicine in France. Following this request, the institution established a steering committee with representatives from national research and clinical agencies, as well as the government and business representatives. Four working groups were also set up, composed of national experts who were tasked with producing detailed reports on the following topics:

1. International situation and 10 years perspectives
2. Innovation and industrial stakes
3. State of the art in France, research and technical applications
4. Infrastructure and organisation

The composition of these working groups and of the steering committee, as well as the tasks they were undertaking, and the recommendations they would make, was kept strictly confidential until the report was published in June 2016.

The final recommendations stemming out of the PFMG2025 [129] are ambitious, and pave the way towards a future where all patients who need it have access to NGS tests, results and follow-up care, regardless of their condition or their location on the territory. It is also a highly collaborative plan, combining research, clinical and industrial expertise to realise genomic medicine in France.

The plan is set around three objectives, namely to "position France among the countries leading the way in personalized and precision medicine", to "prepare for the integration of genomic medicine into the care pathway and the management of common diseases", and finally to "set up a national genomic medicine framework capable of driving scientific and technological innovation, industrial capitalization and economic growth".

More specifically, it warrants the establishment of 12 sequencing platforms throughout the territory, and one National Center for Intensive Calculation (CAD, Collecteur Analyseur de Données) capable of storing, processing and interpreting massive amounts of data to be reported to care providers. In addition, it plans for the creation of National Reference Center for Technology, Innovation and Transfer (centre de référence technologique, d'innovation, d'expertise et de transfert, CRefIX), to ensure that all platforms and the data center stay abreast

of the newest technological developments, and to foster innovation while remaining mindful of the specificities of the French regulatory landscape. It is also dependent on the generalisation of the use of electronic medical records throughout all French healthcare facilities. The plan, which targets for the sequencing of over 200K genomes by 2025, will pilot the use of the platforms with Cancer and Rare disease patients, in alignment with the objectives set out in the Cancer and Rare Disease plans. It will then move on to offer sequencing to patients with common diseases such as diabetes or cardiovascular diseases, to finally offer it to the general population. Its implementation is therefore realistic in the sense that it is incremental, with the two first platforms selected in late 2017[a] [368] after a highly competitive call for projects by the MoH[b]. Instead of creating all infrastructures from scratch, it also leverages existing platforms and local expertise in NGS which have already been active for a number of years in the field of Cancer and Rare diseases. Another particularly noticeable feature of the plan is that it is highly integrated with the particularities of French research institutions, the healthcare system and the industrial network. Although actors who will be charged with implementing planned actions will be selected competitively, representatives from all stakeholders were involved from the inception of the plan. Indeed, among the 14 deliverables listed in the plan, we can highlight three:

"Measure 6: Establish a system to assess and validate new indications for access to genomic diagnosis" will be done in collaboration with the Supreme Health Agency (Haute Autorité de Santé, HAS), patient support groups, General Health Directorate (Direction Générale de la santé, DGS), Social Security Directorate (Direction de la Sécurité sociale, DSS), and will also be based on the collection of empirical evidence, through the support for social science research collecting and analysing experiences from the field.

In "Measure 8: Integrate ethical aspects related to the collection, storage and processing of clinical and genomic data and guarantee a safe, high-quality, care pathway", the creation of a national standard consent form for genomics is planned, as well as the development of a national strategy to deal with incidental findings, as well as a comprehensive legal analysis and harmonization of all provisions applying to clinical genomics.

[a] https://curie.fr/page/plan-france-medecine-genomique-2025-selection-du-projet-seqoia
[b] http://solidarites-sante.gouv.fr/fichiers/bo/2017/17-01/ste_20170001_0000_0069.pdf

We can also note that Measure 12 is dedicated to establishing "a research program dedicated to economic aspects of the Plan", with a cost-benefit analysis for each new indication for NGS testing as it applies to the French social security system.

The FMG2025 plan is therefore a rational, ambitious and well-grounded plan which, if strictly applied, could potentially deliver on it's objective of making France a leader in genomic medicine, for the benefit of patients. Indeed, it largely builds on an already encouraging reality (genomic medicine is effectively available already for many cancer and rare disease patients in France through research) and some steps have already been taken (the two first sequencing platforms were selected and should be operational in the coming weeks). However, some experts doubts that it will deliver on all its promises [369]. The program is already experiencing serious delays from the planned timeline, and the CAD and the CRefIX are not yet created. This may be due to the fact that the most recent presidential elections brought significant leadership changes at the governmental level. Notably, the new health minister Agnes Buzyn is married to Yves Lévy, the author of the PFMG2025 and president of Inserm, one of the leading medical research institute in the country. Although a ministerial order has been signed[a] to leave all matters related to Inserm to the leadership of the prime minister, her direct involvement in the plan could be perceived as a conflict of interest. Indeed, there have been recent allegations that her relationship with her husband have impacted her policies [370] in the allocation of funds to rare disease institutes. Finally, although a commitment of 400 million euros from the government was recently reiterated by the current prime minister in his address following the selection of the two first sequencing platforms [368], the exact way and calendar with which funds will be allocated to realise the specific objectives of the plan is still unclear, and little information is available at this point.

6.3.3.2 Quebec

[a] Décret n° 2017-1088 du 29 mai 2017 pris en application de l'article 2-1 du décret n° 59-178 du 22 janvier 1959 relatif aux attributions des ministres.
https://www.legifrance.gouv.fr/eli/decret/2017/5/29/SSAX1715507D/jo/texte

➢ The Genomic Medicine Policy Landscape in Canada and Quebec

At the Canadian level, four main policy documents can be highlighted, which focus on personalized or precision medicine rather than on NGS per se. These documents demonstrate how Canadian stakeholders perceive the opportunities and challenge of PM since the emergence of this new healthcare paradigm:

On July 30th, 2012, Institute of Health Economics of Alberta published a summary report from a round-table discussion entitled: Personalized Medicine – Policy Gaps and System Readiness.[371] For this discussion, the IHE gathered 19 participants from the Canadian institutes of Health Research, the two HTA agencies INESSS (Quebec) and Canadian Agency for Drugs and Technologies in Health (CADTH Canada), as well as representatives Pfizer and Sanofi, major Canadian Universities and Genome Canada. The objective of the roundtable was threefold: "1. Discuss the current and potential state of the adoption and implementation of personalized medicine in Canada. 2. Articulate some directions, goals and components of a vision for the adoption and implementation of personalized medicine in Canada. 3. Identify opportunities and barriers to achieving these goals and their strengths and limitations." Together, this group identified the lack of coordination between stakeholders such as "payers, providers, patients, and producers of technologies" as the main barrier for implementation of PM in Canada. They suggested to build National Diagnostic Centers or biobanks and focus on low hanging fruits in the field of Oncology, but without providing any detail on where such centers would be located and their exact modus operandi. They also pointed to public-private partnerships as a privileged strategy to strengthen innovation and rapid implementation in PM. Finally, they considered it to be too early to define a Canadian "vision for personalized medicine and genomics".

Two years later, in February of 2014, a new report [7] focusing on health economics and HTA aspects of PM was published by GPS (where genomics, public policy and society meets) GPS is a genome Canada initiative to "facilitate dialogue between federal policymakers and researchers exploring issues at the interface of genomics and its ethical, environmental, economic, legal and social aspects (or GE3LS)". The report, entitled: Personalized Medicine and Health Care Policy: From Science to Value, provides a thorough description of the various socio-economic indicators that should be assessed and balanced when establishing a cost-benefit analysis for new technologies in PM. They mention that PM interventions are particularly difficult to assess because of their multiple biological readouts, their increased uncertainty and the necessity to

balance individual or stratified interests with broader societal values such as solidarity and universal access to basic care. They specifically suggest that the processes of tests regulation and health technology assessment should be better aligned in terms of the evidence needed to assess value and reimbursement opportunities. The need for more coordination between federal and provincial stakeholders, and between provinces is also highlighted. Finally, the report emphasizes the need for more strategic investments in interdisciplinary basic research focusing on technological implementation in health care.

In April of 2014, CADTH produced a report focusing specifically on the cost-effectiveness and clinical use guidelines of next-generation sequencing technologies [372]. In short, after a literature search, the agency concluded that evidence was still lacking on these points, and that available evidence was widely different depending on the specific technology used, and the specific clinical setting in which they were implemented.

Finally, and more recently in June 2016, representatives from Diagnostic Services Manitoba and the CIHR Institute of Cancer Research gathered Canadian "thought leaders" on precision medicine. They published a Consultancy Meeting Executive Summary Report entitled: "Operationalizing Precision Medicine in Canadian Provinces". The switch from personalized medicine to precision medicine is notable, and is reflective of the perspective of industry on the use of terminology. Many of the issues highlighted in this discussion were already mentioned in previous reports, and seem to remain unresolved, such as the need to gather more evidence on clinical effectiveness, for renewed methodologies to establish clinical value and cost utility, more collaboration among stakeholders including regulators and evaluation institutions, and among different provincial strategies. The report however does list a number of existing large-scale initiatives taking place in various Canadian provinces, such as the Genetic Testing Advisory Committees which have been created in Manitoba and Ontario[a], or provincial multi-sectoral endeavors such as the Quebec Network of Personalized Health Care (QNPHC[b]) or the British Columbia personalized medicine initiative[c]. Interestingly, the example of the French Cancer plan was given as a model to follow in the context of oncology. Although the report had a strong

[a] http://www.health.gov.on.ca/en/pro/programs/gtac/
[b] http://qnphc.org/
[c] http://phix.ca/projects/personalized-medicine-initiative-pmi/

focus on cancer precision medicine, it did also mention important scientific advancements in the field of cardiology[a]. Finally, after highlighting multiple successful PM research initiatives, stakeholders involved in the workshop noted that "The rate of scientific discovery is outpacing system capacity and infrastructure to effectively accommodate the adoption precision medicine in clinical practice and public policy, the system is not ready for the tidal wave of precision medicine to come."[371]

Although NGS technologies are only mentioned in passing in these reports, there is a consensus that efforts still have to be made to ensure that all Canadians have access to the benefits of new PM technologies, in a context of a fragmented healthcare system with little federal oversight and inter-province coordination, and more and more limited resources as a result of increased costs and an ageing population.

In Quebec, several documents and reports were also published about PM interventions and their impact on Quebec healthcare.

In October 2014, the commission for ethics in science and technology, (Commission de l'éthique en science et en technologie, CEST) published a report entitled: "Personalized" Health Care: prudence and limitations.

In this report adopting a predominantly precautionary tone, the commission states that it does not believe that personalized health care will revolutionize the practice of medicine, but it does however list a number of ways in which they risk affecting negatively the administration of care to Quebec and Canadian citizens (by complexifying the practice of medicine, and rendering it more technical and collaborative, and affecting the doctor-patient relationship). The main difficulty in interpreting this report is that it addresses issues linked a number of extremely different technologies and practices under one single term: personalized health care. For instance, they discuss the risks of a poor interpretation of genetic testing results in the context of care and direct-to consumer genetic testing in the same terms, however these two contexts are extremely different. They also discuss pharmaco-genomic tests, diagnosis tests and the new design of clinical trials. They also heavily criticize "partner patients" initiatives, in which patients are encouraged to take a more active role in their care by collaborating with medical

[a] http://www.cepmed.com/

doctors in establishing the care trajectory which best fits their personal experience of the disease and their values.

To protect data confidentiality, the commission insists that a strict separation must absolutely be maintained between research and the clinic, and that insufficiently validated tests must never end up in a patient's medical file. Their first recommendation is to ensure that principles of clinical utility and scientific validity are established before a test is implemented in the clinic. The report lists a total of 9 recommendations which are quite specific, in order to ensure that the quality of care offered to patients is of the highest possible standards, that the population is informed of potential limitations of personalized health care, that professionals are properly trained to interpret genetic information, and that any new use of innovative or expensive technology or treatment is done while respecting the government's mission to provide the population with high quality, universal and accessible health care. They also recommend that measures be taken to ensure the protection of patients and citizen's privacy and personal data confidentiality, and avoid genetic discrimination.

In October 2015, the QNPHC published a report entitled : « Integration path for diagnostic tests in personalized health care in Quebec : welcome tomorrow's medicine. » [373]

In this report, it provides a detailed description of the certification, evaluation and reimbursement processes which have to take place in order for personalized healthcare diagnostic tests to be implemented in the care trajectory of Quebec Citizens. At each level, authors identified issues and hurdles that PM intervention developers and users could face. Certification, which is provided by Health Canada, is necessary for all medical tests or devices to be commercialized in Quebec, and includes respect of applicable ISO norms, but there is no specific norm relative to genomics. As long as they harbor a genetic component, PM devices are considered a class III medical device.[a].

At the level of evaluation, which in Quebec is done by INESSS, they notably pointed to the difficulty of proving clinical utility and cost-efficiency without having access to real-world

[a] Laboratory-developed tests do not need to obtain this certification, although in the US, the FDA has recently demonstrated an interest in generating oversight guidance for LDTs as well, which has generated a lot of debate[414–420], although no firm decision has been taken on this following the consultations and discussion which took place between 2014 and 2017[421].

evidence data in the context of the Quebec healthcare system. In addition, because of the ethical and legal implications of PM intervention, linked to the risk of genetic discrimination and the need to control the access to personal patient data, the perspectives of a multitude of stakeholders should be taken into account in the evaluation process, which is complex and costly. Finally, because demands for evaluation can only be submitted by the ministry or by professionals associated to public hospitals or laboratories, these stakeholders need to be better informed and educated about PM. More generally, the report suggests that all stakeholders including patients, medical professionals, and healthcare administrators, have an important role to play in the implementation of PM interventions in the healthcare system, and therefore a significant information dissemination effort should be made throughout the province. By detailing all the hurdles, the clear objective of the report is to facilitate the development and use of PM interventions, and to demonstrate their benefits and positive impact on the healthcare system efficiency.

The same month, a report was published by the Center for Interuniversity Research and Analysis of Organizations (Cirano), entitled: "Quebec as a leader in the development and integration of personalized healthcare: Do current regulation and policies allow this?" [374]. This report, whose underlying research was funded by the QNPHC, follows a similar approach than the previous report, with the addition of an international comparison of Quebec with 12 other Canadian and international jurisdictions. The report's findings partly overlap with that of the previous report, and are as follows:

The authors identified four main limits to the implementation of PM diagnostic tests in Quebec:

- The fact that RAMQ essentially only reimburses tests which are realised within provincial hospital institutions, and not private companies, and the absence of regulation allowing the offer of diagnostic tests realised within Quebec private laboratories. They therefore recommend that in case a test is not offered in a Quebec hospital laboratory, but is requested by a medical doctor, a procedure be put in place so that tests offered in other contexts in the province be reimbursed.
- The absence of an evaluation procedure based on the continuous collection of evidence, which should be established in order for innovative personalized medicine intervention to be accessible in Quebec.

- The impossibility for private technology developers to submit an evaluation request directly to the Ministry of Health and Social services.

➢ Health technology assessment and the role of INESSS

In Quebec, all available medical biology tests, and the laboratories where they are available, are listed in a "repertoire" available online[a]. Decisions regarding adding or removing tests from the list, or redistributing the testing responsibilities among hospitals are taken by the Ministry of Health and Social Services (MoHSS). They usually follow recommendations from the Quebec Health Technology Assessment Institution, INESSS (National Institute for Excellency in Health and Social services) INESSS was created in 2011, and is regulated by law[b]. Its mission is to "to promote clinical excellence and the efficient use of resources in the health and social services sector"[c]. It notably assesses "the clinical advantages and the costs of the technologies, medications and interventions used in health care and personal social services. It issues recommendations concerning their adoption, use and coverage by the public plan, and develops guides to clinical practice in order to ensure their optimal use."[d]

Reports from INESSS on new biomedical tests can be requested through two distinct procedures: Either directly from the MoHSS, or by a group of professionals, researchers and/or medical practitioners representing a public laboratory, who submit proposals with scientific evidence in support of a new test. When a request is submitted, INESSS's permanent scientific committee on medical biology analysis goes through the assembled evidence, and assesses the clinical utility, clinical validity, analytical validity as well as costs, organisational and ethical implications of the new test. The assessment is conducted by the committee itself who can request advice from professional experts. The role and composition of the committee can be found on INESSS's website[e]. If the committee finds that the new test does provide advantages, or has an added value compared to standard of care, it will make a recommendation to the

[a] http://www.msss.gouv.qc.ca/repertoires/biomed/
[b] Loi I-13.03 sur l'institut National d'Excellence en Santé et en Services Sociaux
[c] https://www.inesss.qc.ca/en/about-us/about-the-institut.html
[d] https://www.inesss.qc.ca/en/about-us/about-the-institut.html
[e] https://www.inesss.qc.ca/en/about-us/structure/standing-scientific-committees/comite-scientifique-permanent-des-analyses-de-biologie-medicale.html

MoHSS to add it to the repertoire. The Ministry then usually follows that recommendation, and determines which institution(s) will offer the test, and organises its reimbursement through the provincial medical insurance system, RAMQ (Regime d'Assurance Maladie du Québec).
If a test that is not available in the repertoire is prescribed to a patient by a medical doctor in the province, it can be offered to the patient, and reimbursed by RAMQ through a special "out-of province test" procedure request. However, the MoHSS also publishes a list of tests that are not to be reimbursed through this procedure. This list, entitled « list of analyses not covered by Quebec medical insurance and not reimbursed in the framework of the Authorisation and reimbursement mechanism for medical biology analyses not available in Quebec »[a] is updated annually and sent to all 15 public healthcare institutions hosting certified laboratories in the in the province. The decision to add a test to this list is based on recommendations from INESSS, or from other advisory institutions such as provincial newborn screening committees. Although the exact status of this list is unclear (it is not directly available on the Ministry's website), some hospitals publish it online to inform patients and the medical community of all tests that are unavailable for reimbursement.

Until 2014, WES was available for reimbursement through the out of province test special request. DNA from patients was hence sent to laboratories in other provinces or in the USA for testing, resulting in significant costs bared by RAMQ. (several million dollars per year). In addition, in 2014 INESSS published a recommendation not to introduce WES for diagnosis of intellectual disability and neurodegenerative diseases to the repertoire [327]. Indeed, they found that there was insufficient evidence of clinical validity of WES, and that the need to confirm variants by sanger sequencing was an indication of insufficient analytical validity for certain exomic regions. As a result, WES was added to the "non-reimbursable" tests list in 2014, but as a whole, preventing its use for any medical indication. Further, INESSS also found that the use of NGS in Cancer was not ready for clinical implementation [328], and that neither were gene panels specifically designed to detect hereditary cancers [375] or to offer personalized treatment

[a] Liste des analyses non couvertes par l'assurance maladie du Québec et non remboursées dans le cadre du Mécanisme d'autorisation et de remboursement des analyses de biologie médicale non disponibles au Québec, Réf. : Circulaire 2011-12.

options[376]. As a result, "all gene panels covering 3 diseases or more (ex: MyRisk™, OncoGeneDx Custom panel, Invitae Common Hereditary Cancers panel, FondationOne, FondationOne Heme, etc.)" were also added to the non-reimbursable tests list. Since 2015, there have been discussions on potentially reforming INESSS, and creating a new unit dedicated to genetic and genomic medicine, in order to enable the evaluation process to be more rapid and more adapted to technological developments in genomics, but no official steps have been taken in this direction so far.

Since 2014, patients have access to NGS only through research projects, such as Care4rare, a pan-Canadian initiative offering NGS to patients with undiagnosed diseases. In Quebec, there have been significant investments in genomics research, with the McGill University Genome Innovation Center acquiring Illumina HiSeq X with the capacity to sequence 9,000 whole genomes per year. However, this infrastructure is not certified to perform clinical tests. In addition, an investment of $255 million by federal and provincial governments in genomics research and infrastructure was announced in January 2018[a], through a partnership with Genome Canada, Genome Quebec and Calcul Quebec. A Canadian Centre For Computational Genomics (C^3G)[b] was also funded by Genome Canada in 2016, to enable genomics data to be stored and processed, for research and potentially for the clinic as well, under the Ontarian model of the HPC4Health initiative, offering centralized and secure clinical data storage and processing infrastructure to multiple hospitals in the province[c].

➢ A National Genomics plan in construction.

There are currently seven supra-regional institutions that offer molecular genetics test to patients throughout the province, namely: McGill University Health Center, Ste Justine University Hospital, University of Montreal Hospital Center, Jewish General Hospital, Maisonneuve-Rosemont Hospital, Quebec University Hospital, and Sherbrooke University Hospital Center. In

[a] https://www.genomecanada.ca/en/news/canadian-patients-benefit-major-investment-genomics-and-precision-health-research
[b] http://www.genomequebec.com/canadian-centre-for-computational-genomics-c3g.html
[c] http://www.hpcforhealth.ca/

2015, the Minister of Health sent a letter to all seven institutions asking them to propose a province-wide solution to offer clinical genomic testing to Quebec patients. Following this request, all seven institutions as well as Genome Quebec submitted a proposal to create a national consortium with one centralized clinical sequencing platform, located in Ste Justine, and a distributed data analysis and reporting strategy. All members of the consortium listed disorders that they would like to be responsible for, with the understanding that requests for sequencing, and data interpretation and return of results would be done within their institution, regardless of the provenance of the patient. The decision for the sequencing platform to be located in Ste Justine is mainly based on the fact that in October 2014, they have announced the creation of an Integrated Clinical Genomic Centre In Pediatrics[a], in partnership notably with Genome Quebec. The platform, based on the Illumina 2500 technology, started functioning in the summer of 2015 by offering sequencing services to researchers in Ste Justine and other institutions in the province, and is in the process of obtaining CLIA and ISO certification to be able to offer clinically validated tests.

According to discussions with Quebec experts in clinical genomics conducted in the framework of previous research we conducted on the topic[3] , the consortium proposal seemed to have been approved unofficially by the Ministry. However, no official decision has been taken so far to put it in place. The delay in this decision could be explained by the fact that the Ministry has been investing significant resources in two major reorganization projects, one focused on the healthcare institutions network in 2015[b], and one focused on medical biology laboratories, OPTILAB, launched in 2011[c].

6.4 Discussion and conclusions

The objective of our study was to provide a critical contemporary overview of the governance framework relevant to clinical genomics in France and Quebec. Our method was focused on the

[a] http://www.genomequebec.com/en/centre-de-genomique-clinique-pediatrique-integre-genome-quebec.html
[b] http://www.msss.gouv.qc.ca/en/reseau/reorganisation/
[c] http://www.msss.gouv.qc.ca/professionnels/soins-et-services/optilab/

collection of documents, and was based on discussions with technology users, however we did not have an opportunity to formally discuss with decision makers within professional associations or the ministries of health, which may have given us another perspective on the topic. Finally, most of the policy documents we found were published after the search started in 2014, which indicates how much the policies in clinical genomics are in flux. It could be seen as a limitation, since many decisions remains to be made, and the evidence on clinical utility and cost efficiency is being collected.

Citizens and patients in France and Quebec are protected by a normative framework which ensures the respect of certain fundamental rights. Access to healthcare in both countries is universal and does not depend on capacity to pay[a]. Informed, express and revocable consent has to be collected in order for individuals to undergo genetic testing, be informed of results, and participate to research, and in order for researchers and healthcare professionals to use their sample and data[b]. Independent research ethics committees review protocols in order to ensure that research is conducted while respecting patients and participants' rights[c]. Genetic discrimination is prohibited in both France[d] and Canada[e]. The genetic tests patients may have access to in the context of care can be prescribed and interpreted only by certified professionals, and can only be conducted in a controlled laboratory environment to ensure they are of the highest possible quality. The implementation of WES or WGS-based tests, as opposed to targeted tests, does not cause significant threat to this long-established protective framework. However, these tests do demand an adaptation of existing laboratories, research and healthcare infrastructures[1], and their cost-effectiveness is extremely difficult to establish outside of small-scale selective applications[88]. But clinical genomics is a reality, and both France and Quebec have demonstrated expertise in this domain, excellent research capacities, and have invested significant resources in the most advanced technologies in NGS. The need to train healthcare professionals in genomics, and to train more bioinformaticians and genetic counsellors has been

[a] Public Health Code, Article L. 111-2-1 in France and Article 7 of the Canada Health Act for Quebec.
[b] Civil code, article 16-10 to 16.13 in France and Civil Code of Quebec, article 11.
[c] Public Health Code, Article L1123-6 in France and Civil Code of Quebec, article 24.
[d] Loi n° 2002-303 du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé, articles 4, 98 and 99.e
[e] Genetic Non-Discrimination Act, S.C. 2017, c. 3

recognized for several years by a number of stakeholders[1,234,377,378], and steps are being taken in order to tackle some of these issues. For instance, Quebec has been collaborating with the UK National Health Service health education branch to design a course on medical genomics for healthcare professionals, available since early 2018.[a]

However, the translation of these technologies to healthcare is still in process and is facing a number of hurdles. In France, patients already have access to the technologies in the context of research projects and there is a demonstrated political will to implement medical genomics, as demonstrated by the PFMG2025. However, there are already a number of delays from the planned schedule, and it remains to be seen how the funding will be actually distributed. Some marginal legal adaptations have to be implemented in order for NGS technologies to be used smoothly in the clinic; such as the language used to describe the consent process for genetic testing in the French law[b]; but they don't constitute significant hurdles. France is also currently in the process of revising its Bioethics Laws, and has launched a nation-wide public consultation on a number of topics, including genomic medicine[c]. The legal review resulting from these debates will certainly have a significant impact on the implementation of genomic medicine in France.

In Quebec, the law is more succinct than in France, and does not specifically mention genetic information or genetic testing. It is rather at the level of the evaluation and reimbursement process that adjustments have to be made, in order for patients to have access to NGS-based tests. First, the HTA process involving INESS needs to be adapted in order for the clinical utility, analytical validity and cost utility of such tests to be established. Second, Quebec needs to propose a framework to enable private developers to submit tests for evaluation. Finally, the ministry of health still needs to make an official decision on the creation of a national consortium in clinical genomics involving all relevant stakeholders throughout the province. In the

[a] http://rsspq.org/nouvelles-rsspq/entente-tripartite-avec-le-royaume-uni-le-quebec-prend-le-virage-de-la-formation-specialisee-en-genomique/

[b] Arrêté du 27 mai 2013 définissant les règles de bonnes pratiques applicables à l'examen des caractéristiques génétiques d'une personne à des fins médicales

[c] https://etatsgenerauxdelabioethique.fr/

meantime, proof-of concept research projects are being funded by private foundations to continue to offer tests to patients and demonstrate their clinical utility and cost-efficiency[a].

In conclusion, we did not find strong evidence that there were unsolvable legal barriers impeding the responsible implementation of clinical genomics in France and Quebec. However, HTA and reimbursement policies have to be adapted in Quebec, and tests will not be accessible outside of research projects until the Ministry of Health approves the creation of a national genomics consortium, which currently blocks the progress of the implementation process. In France, the political will is present, but the landscape may evolve towards the definition of more or less ambitious goals in medical genomics depending on funding distribution and the outcome of the revision of the bioethics laws.

[a] Exemplified by the recent launch of the SIGNATURE project, aiming to offer WES and RNAseq to 200 newly diagnosed pediatric cancer patients throughout the province. (confidential)

CHAPTER 7: CONTRIBUTIONS TO THE FIELD AND DISCUSSION

7.1 Contributions to the field

7.2.1 Introduction

In this thesis research project, our objective was to contribute to the body of evidence available to policy makers on the clinical implementation of NGS in France and Quebec. We therefore collected evidence from the published literature (Chapters 2 and 3), and from the "real-world" use of NGS in French and Quebec teams (Chapters 4 and 5). Finally, in light of these results, and in order to better document the challenges of implementing NGS in clinical care in the area of oncology and for rare diseases in France and Quebec, we conducted an analysis of the applicable regulatory landscape (Chapter 6).

7.1.2 Chapter 2

In Chapter 2, we conducted a systematic literature review, which was the first study published providing both a quantitative and qualitative overview of unsolved issues reported directly by NGS early adopters. We identified 23 issues reported by technology users on the use of NGS in the clinic. These issues arise at each step of the process, from data production, to data analysis, reporting and sharing. The most consistently reported issues, across all disease types and countries, were the handling of incidental or secondary findings (IF), the interpretation of variants, or addressing variants of unknown significance (VUS), and finally issues of cost and reimbursement. We also noticed that technology users were calling for guidelines to be published before WES could replace more targeted genetic tests, which could not be done without important financial investments and infrastructural adjustments in the healthcare system.

7.2.3 Chapter 3

Because we noticed that most patients whom had access to NGS in the context of their care were children, we re-analysed our systematic literature review data, focusing on the pediatric context. Three salient categories of issues were identified: First, because consent is given on children's behalf by parents or legal guardians, decision making processes are more complex than in the case of a person deciding on their own. Many complex questions have to be addressed in the pre-test counselling sessions, such as the categories of results to be reported. Indeed, incidental findings may have heavier or more direct consequences on parents than on the child being tested. Finally, turnaround time is particularly critical when current or future pregnancies are at stake. Since we found that several guidelines had been published by American, Canadian and European professional associations, we evaluated how these guidelines addressed the issues raised by technology users. We found that many of the issues listed, such as who to offer WES to, the information to provide in counselling sessions, variant interpretation, return of results or data sharing strategies, were addressed by the guidelines. However, these guidelines remained quite general, leaving many implementation decisions to the responsibility of professionals, whether they are the clinicians ordering the tests, the clinical geneticists interpreting the results or the laboratories establishing analysis and reporting strategies.

7.2.4 Chapter 4

These professionals were hence the focus of our fourth chapter, in which we conducted a multiple case study analysis of early NGS adopters in four clinical settings in France and Quebec. Building from results from Chapter 2 and 3, we sought to identify the main challenges they had faced in implementing NGS technologies, and have them describe their vision for the future. Because the evidence we analysed in Chapters 2 and 3 was mostly from teams operating in the USA, in the context of a heavily privatized healthcare system, it was particularly interesting to get insights from France and Quebec, where access to care is universal and heavily subsidised by the government. In addition, using the case study method allowed us to have access to a more granular level of information on how teams operated than we would have through simple surveys or interviews. Confirming our findings from Chapters 2 and 3, we found that the main challenges teams faced in setting up clinical NGS were linked to the complexity of

the data, and the infrastructure needed to produce, store, analyse and interpret it. Indeed, both the bioinformatics processing and the clinical interpretation of NGS data required the intervention of multiple professionals with complementary training and experience in informatics, genetics and a deep clinical knowledge of the patient's phenotype. Second, according to our participants, a responsible use of technologies required that more clinicians be trained in genomics and that they develop a better understanding of the advantages and limitations of NGS. This, and the need to train more bioinformaticians, was already highlighted as important challenges in our systematic literature review. However, several participants also mentioned that members of government and HTA agencies also had to be trained in genomics, and that this lack of training was partly responsible for what was perceived as a suboptimal clinical translation process of NGS. More generally, we found that stakeholders expressed the need to get buy-in, not only from clinicians (as already identified in Chapters 2 and 3) but also from governmental stakeholders, especially from members of the Ministries of Health of each of the two countries studied. The need for this high-level political commitment in order for NGS to be implemented in the clinic was a novel finding, of highly specific local relevance in France and Quebec. This would have been difficult to uncover without having obtained the trust of stakeholders through the case study method. Indeed, because government officials and agencies are decision makers who have a strong impact on the allocation of funds, it can be challenging to obtain and analyse criticisms against them from stakeholders who may have a lot to lose by openly providing this information. Regarding their vision for the future, stakeholders highlighted important and rapid technological developments, which would increase the accuracy and clinical relevance of WES, and decrease the cost of storing and analysing WGS data. They also had a rather positive outlook on the next few years, and expressed that they believed many of the issues they had identified would be solved within five years. They foresaw that NGS would gradually be used in a broader range of conditions, in addition to cancer and rare diseases.

7.2.5 Chapter 5

The case study method also allowed us to explore in depth the transition of NGS from the research to the clinical realm. Indeed, when describing their projects, the teams we worked with identified a number of organisational features that pertained clearly to both realms. Research was sometimes portrayed positively, as a way to gather more biological knowledge and improve

clinical analysis methods. However, some participants described research as a "a necessary temporary step before WES is validated as a clinical test and reimbursed by the government"[4]. We explored this theme more deeply in Chapter 5, in which we also conducted a legal analysis of the frameworks applicable to research with human subjects, and care in France and Quebec. We identified several elements which justify why NGS have a particularly blurry status between research and care. Most importantly, NGS data has an increased collective value when it is shared broadly, and allows for an increased understanding of disease. In addition, the status of the information it contains evolves overtime, as more people are sequenced and the knowledge-base in genomics expands. This blurry status does not necessarily imply that clinical NGS poses a threat to patients' and participants' privacy and autonomy. Indeed, we identified bridges between the legal frameworks applying to care and to research, because they are both protective of the rights of patients and participants.

7.2.6 Chapter 6

In chapter 4, we concluded that "more research is needed on the legal and regulatory frameworks specifically applicable in both regions, taking the specificities of each healthcare system, legal landscape, and demographics into consideration."[3] This is what we focused on in our final research Chapter. Indeed, after having collected evidence from the literature and from the field, we conducted an analysis of the regulatory frameworks applicable to medical genomics in France and Quebec. In line with our findings in Chapter 5, we found that the network of international declarations, national regulations and regional policies applicable to date provide a number of protections to patients and participants. In France, the production, analysis, reporting and sharing of genetic data is strictly framed in the law. The law in Quebec does not mention genetic data specifically, however in both France and Canada, principles are established in order to protect citizens against their potential misuse, in genetic discrimination for instance. We found no strong evidence that wide legal or policy gaps would let clinical genomics present important risks for generalized harm to patients and participants. However, the establishment of national clinical genomics plans in both France and Quebec require a number of procedural and infrastructural adjustments, notably in large scale education in genetics and genomics, in readjusting the responsibilities of healthcare professionals and genetic counsellors, in health technology assessment procedures and cost analysis methods. In this chapter, we also explored

recent policy developments in France and Quebec which have the potential to significantly impact the field. Although France has demonstrated a strong political will to implement clinical genomics with the publication of a medical genomics national plan in 2016, uncertainties remain regarding its funding and overall progress. In addition, a national consultation is underway in order to revise the bioethics laws, and citizens will have a chance of expressing their hopes and fears regarding the use of NGS-based tests in care. In Quebec, no public announcement has been made to date to establish such a large-scale medical genomics plan. However, through the research conducted in Chapter 4, we were able to identify and describe ongoing debates which indicate that a decision may be made soon to reform HTA processes and offer clinical WES to certain patients through regional hospitals. To our knowledge, this study is the most comprehensive review available to date on legal and policy frameworks of the use of NGS in the clinic, applicable in both France and Quebec.

7.2 Discussion

7.2.1 Main issues with clinical NGS

Since we conducted our systematic literature review, numerous reports of clinical use of NGS have been published, in a variety of clinical settings and countries, including France[43,92,124] and Quebec[78,127]. Although many teams still use WES[80,90,379], a growing number of them now also use WGS [69,380,381], which in some contexts is reported to outperform WES[382,383]. Technical improvements have been massive in both techniques, at the level of data production, processing, and bioinformatics analysis[287,384–388]. It would therefore be interesting to perform the search again and see if some challenges have been solved and/or if others have appeared.

7.2.1.1 Variants interpretation

In our review, the number of selected articles reporting issues with IF steadily increased with publication year, whereas that number decreased for VUS and variants interpretation. Although we had a small number of articles in the first and last years (13 in 2011, and 12 in 2015), it would be interesting to see if this trend continued or evolved since 2015. Indeed, as we identified in Chapter 6, numerous professional guidelines were published covering both topics, indicating

that consensus has been reached on solutions to solve these issues. However, it seems like variant interpretation, and the strategies needed to filter results based on their clinical utility and actionability is still one of the major unsolved issues in clinical genomics. Indeed, even when guidelines exist, their application may still be difficult and context-dependent[237].

7.2.1.2 Cost-efficiency and clinical utility

As identified in Chapter 6, there is still an unresolved controversy and an overall lack of evidence over the actual cost-efficiency of NGS tests as opposed to standard of care, or more focused genetic tests[88]. Another unresolved issue is the definition of the clinical value, or clinical utility of NGS tests[238]. Indeed, it is highly clinical context-dependent. As we have seen in Chapter 4, in the context of rare diseases, the main outcome measured is the provision of a molecular diagnosis explaining symptoms observed in a patient. Diagnosis is not always directly associated with reduced disease burden, and to date, a majority of rare diseases remain without a cure[389]. However, obtaining a diagnosis has been shown to provide multiple other benefits, such as "as adapting care, preventing complications, offering new treatments or participation opportunities in clinical trials, and genetic counselling for the family."[3] In the context of cancer, NGS is generally used to identify driver mutations that could be targeted by pharmacological agents in order to slow or stop oncogenesis. The use of this "targetable mutations" identification as an outcome measure has been heavily criticized because it is only poorly related with patient overall survival or lower cancer morbitity.[106] However, NGS data from patients, if shared widely in the research community, have the potential to increase our knowledge-base on diseases and provide important societal benefits[276,329,390]. Therefore, many authors have suggested that evaluating the benefits of NGS techniques required the design of new strategies to evaluate clinical utility, with more holistic view of benefits and value, not only at the individual patient level, but also at the collective, societal and global levels[20]. Unfortunately, evidence is still largely lacking in this domain[391].

7.2.1.3 The learning healthcare system

Necessary changes have been highlighted in the delivery of healthcare, with a tighter link between research and care, and the switch to a research-based care model[4]. Clinical implementation of NGS can happen simultaneously with the collection of evidence, (coverage

with evidence development[392–395]) following the model of a "learning healthcare system"[52,396,397], which continuously collects evidence for practice and delivery improvement, going beyond the evidence-based policy approach described in the introduction.

In the United States, strategies of implementation and reimbursement with evidence collection have started to be used in clinical genomics[6,14], both in cancer[398,399] and rare diseases[a]. As we showed in chapters 4-6, the situation is different in France and Quebec, where still to date, NGS is available mostly through research or proof-of-concept programs.

7.2.1.4 Liability

In light of the recent Williams vs Athena/Quest trial ongoing in the United States, where a mother sued a laboratory for failing to report the change of status of an incidental finding in her son[400–403], an issue which could be mentioned is the potential impact of genomics on liability risks for clinicians, laboratory personnel and genetic counsellors. It would be important to determine if and how this could impact Quebec and French courts, and there is little evidence to date on this matter[358].

7.2.2 Guidelines implementation

In Chapters 3 and 6, we identified a number of policy guidelines which were published over the years to frame the implementation of NGS technologies in research and in care. We found that some technology users may not always be aware of existing guidelines[2], or that they may have an unclear perception of what they imply in practice[4]. However, the direct focus of our research was not to test the impact of guidelines on practices. It would be very interesting to observe and assess the implementation of guidelines such as the ones published by American professional associations, which we identified in Chapter 6, on variants interpretation[347], reporting secondary findings[346], or bioinformatics pipelines[348]. Indeed, as a recent review demonstrated, there is little evidence available on how guidelines are actually implemented in care[34]. This implementation trajectory in the field of NGS could be compared to that of other genomic technologies such as

[a] https://www.bluecrossnc.com/sites/default/files/document/attachment/services/public/pdfs/medicalpolicy/whole_exome_and_whole_genome_sequencing_for_diagnosis_of_genetic_disorders.pdf

Array CGH[293,404], or other non-genetic technologies, for instance in the field of newborn screening[405–407].

7.2.4 Observing policy decisions in the making

In this project, we aimed at producing evidence which could be used by policy makers when making clinical NGS implementation decisions. Indeed, some policy institutions do look at result from academic research, as exemplified by the recent publication from the CNIL in France, which cited several doctoral theses in their most recent book on genetic data[408]. In Chapter 6, we identified policy documents which made recommendations based on evidence collected from various sources, whether from published research, interviews with experts or field visits. As we identified in Chapters 4 and 6, critical decision makers in clinical genomics are members of the ministries of health and other governmental agencies in charge of HTA. It would therefore be interesting to interview relevant members of the Ministries of Health, of INESSS in Quebec or the ABM in France, in order to determine what kind of evidence they based their decisions on. One could, for instance, ask the French ex prime minister Manuel Valls to detail the reasons behind his decision to ask Aviesan to produce the FMG2025 report. Similarly, one could interrogate the Quebec Minister of Health Gaétan Barrette, or the Deputy Minister Mr. Michel Fontaine about their decision to send a call for proposals to all Quebec supra-regional laboratories in order to organise the offer for clinical genomics services in the province. Identifying not only the evidence they based these decisions on, but also how they balanced genomics with the numerous other priorities for the nation, would be crucial in order to determine why and how clinical genomics made its way to the highest levels of government. It would for instance be exciting to determine the impact of other countries' announcements, such as the UK (100.000 genomes project) and the US (Obama's precision medicine initiative) on France and Quebec's political decisions. Indeed, as we identified in Chapter 4, stakeholders in both nations expressed fear, regret or disappointment with "being late" compared to others. (Appendix C, Additional file 3). Indeed, their perception is that this means patients in France or in Quebec are losing out on an opportunity to get better care, as compared to patients in the US, in the Netherlands or elsewhere. In the political discourse too, the importance of maintaining or regaining the nation's leadership in this domain is clear. In France, for instance, the first objective of the FMG2025 plan is to "position France among the countries leading the way in

personalized and precision medicine". Indeed, failing to ensure France's leadership in this "global competition" could lead to "losing important ground in terms of both French economy and health care system."[129] In addition, the perspective of patients and that of popular media may also weigh heavily on these decisions. Since Quebec politicians have not yet published their official position on the matter of clinical genomics, it would be particularly interesting to interrogate them and really observe policy decisions in the making. Several studies have been conducted observing the uptake of evidence in health policy decisions in Belgium[13] and more recently in six European countries (excluding France)[15]. Similar methodologies could for instance be used in the context of clinical genomics in France and Quebec. A related theme which could be explored further is that of the "technological imperative"[409,410]. Indeed, different stakeholders in France and Quebec, including patients and families, policy makers, and healthcare professionals could be asked if they think that because the technology is available, there may be a moral imperative to use it, or only to evaluate whom it can be useful for at an acceptable social, ethical or financial cost.

CHAPTER 8: CONCLUSIONS AND FUTURE DIRECTIONS

In this research project, we have collected evidence on the clinical use of NGS technologies, and the issues this might represent for the French and Quebec healthcare systems from the perspective of expert technology users. We have shown that because they require significant investments and represent a paradigm shift towards the delivery of a research-informed care, their implementation could not be done without strong political commitments. We can safely assume that genomic sequencing will never become a "black box", and that the correct interpretation of genomic data will always require the intervention of interdisciplinary experts. Indeed, recent projects such as the personal genome project Canada[117,118] have shown that sequencing a healthy population makes us realize how much uncertainty there still is in interpreting variants. In addition, a growing number of studies show that the correct clinical interpretation of genomic variants may drastically change depending on the patient's ethnicity[411,412]. At a stage when still most people who have been sequenced are from European descent[413], it is urgent to correct this bias in order to provide an equal quality of care to all populations. Medicine remains an art, which is now performed collectively, and with the help of advanced and highly technical tools, such as NGS technologies. But communicating the incredibly complex information carried by a patient's genome should always be done while being mindful of the specific patients' experience, cultural background, level of education, family dynamics, and beliefs. This cannot be done without the intervention of properly trained individuals in genetics and genomics counselling, more of whom will need to be trained in the future. If there is no moral imperative to use technologies, especially when their clinical utility and cost efficiency are still being established, we can argue that there is a moral imperative to use it first in those who need it the most, rather than in those who can afford to pay for it. More research is definitely needed in this domain, but I believe there definitely is a moral imperative to start by sequencing the sick before sequencing the healthy, especially when it is paid for by the public funds.

This project has focused on France and Quebec, who are relatively late in clinical genomics implementation, as compared with the US, the UK, the Netherlands, Germany or Estonia who "have already committed to making genomic medicine part of their health care systems in various ways"[129]. However, we did not perceive this has had strong negative impacts. Indeed, many patients have had access to the technologies in the context of research, and the design of nation-wide policies is being informed by the results of initiatives taken elsewhere. Both France and Quebec are hence able to learn from previous experiences, and have the ability to take this opportunity to design well-informed, locally adapted policies.

Finally, this research project has been a highly interdisciplinary one. Indeed, it has required proficiency in human genetics, as well as in public policies and qualitative analysis methods. The success of this project has greatly benefitted from our affiliation to two social science research teams embedded in biological sciences university departments. However, it is still a challenge to convey such interdisciplinary results to single-disciplined audiences, whether in scientific conferences or in academic journals. Indeed, social or natural sciences audiences have widely different expectations, in terms of methodological design and implications of the results in their field. There is still significant progress to be made in the support for interdisciplinary training and research, which I believe can bring important insights, especially in the field of health policy.

REFERENCES

1. Bertier, G., Hétu, M. & Joly, Y. Unsolved challenges of clinical whole-exome sequencing: a systematic literature review of end-users' views. *BMC Med. Genomics* **9,** 52 (2016).
2. Bertier, G., Sénécal, K., Borry, P. & Vears, D. F. Unsolved challenges in pediatric whole-exome sequencing: A literature analysis. *Crit. Rev. Clin. Lab. Sci.* **54,** 134–142 (2017).
3. Bertier, G. & Joly, Y. Clinical exome sequencing in France and Quebec: what are the challenges? What does the future hold? *Life Sci. Soc. Policy* **14,** 17 (2018).
4. Bertier, G., Cambon-Thomsen, A. & Joly, Y. Is it research or is it clinical? Revisiting an old frontier through the lens of next-generation sequencing technologies. *Eur. J. Med. Genet.* **61,** 634–641 (2018).
5. Davis, D. *et al.* Learning in practice The case for knowledge translation: shortening the journey from evidence to effect Concepts of CME and CPD. *BMJ* **327,** 33–5 (2003).
6. National Academies of Sciences Engineering and Medicine. *Applying an Implementation Science Approach to Genomic Medicine*. (National Academies Press, 2016). doi:10.17226/23403
7. McCabe, C. & Husereau, D. Personalized Medicine and Health Care Policy: From Science to Value. *GPS Where Genomics, Public Policy Soc. Meet* (2014).
8. Tsimberidou, A. M., Ringborg, U. & Schilsky, R. L. Strategies to Overcome Clinical, Regulatory, and Financial Challenges in the Implementation of Personalized Medicine. *Am. Soc. Clin. Oncol. Educ. B.* **33,** 118–125 (2013).
9. Bombard, Y., Bach, P. B. & Offit, K. Translating genomics in cancer care. *J. Natl. Compr. Cancer Netw.* **11,** 1343–1353 (2013).
10. Young, S. P. *Evidence-Based Policy-Making in Canada*. (Oxford University Press, 2013).
11. Cookson, R. Evidence-based policy making in health care: what it is and what it isn't. *J. Health Serv. Res. Policy* **10,** 118–121 (2005).
12. Baicker, K. & Chandra, A. Evidence-Based Health Policy. *N. Engl. J. Med.* **377,** 2413–2415 (2017).

13. Van Herck, P., Annemans, L., Sermeus, W. & Ramaekers, D. Evidence-Based Health Care Policy in Reimbursement Decisions: Lessons from a Series of Six Equivocal Case-Studies. *PLoS One* **8,** e78662 (2013).
14. Embi, P. J. & Payne, P. R. O. Evidence generating medicine: redefining the research-practice relationship to complete the evidence cycle. *Med. Care* **51,** S87-91 (2013).
15. van de Goor, I. *et al.* Determinants of evidence use in public health policy making: Results from a study across six EU countries. *Health Policy (New. York).* **121,** 273–281 (2017).
16. Gupta, M. Improved health or improved decision making? The ethical goals of EBM. *J. Eval. Clin. Pract.* **17,** 957–63 (2011).
17. Birko, S., Dove, E. S. & Özdemir, V. A Delphi Technology Foresight Study: Mapping Social Construction of Scientific Evidence on Metagenomics Tests for Water Safety. *PLoS One* **10,** e0129706 (2015).
18. Timmermans, S. Trust in standards: Transitioning clinical exome sequencing from bench to bedside. *Soc. Stud. Sci.* **45,** 77–99 (2015).
19. Green, R. C. *et al.* Clinical Sequencing Exploratory Research Consortium: Accelerating Evidence-Based Practice of Genomic Medicine. *Am. J. Hum. Genet.* **98,** 1051–1066 (2016).
20. Husereau, D. Changing HTA Paradigms. (2016).
21. Knoppers, B. M. Does policy grow on trees? *BMC Med. Ethics* **15,** 87 (2014).
22. Chanturidze, T. & Obermann, K. Governance in Health – The Need for Exchange and Evidence Comment on 'Governance, Government, and the Search for New Provider Models'. *Int. J. Heal. Policy Manag.* **5,** 507–510 (2016).
23. Pokorska-Bocci, A. *et al.* 'Personalized medicine': what's in a name? *Per. Med.* **11,** 197–210 (2014).
24. Bauchner, H. & Fontanarosa, P. B. Health Care Spending in the United States Compared With 10 Other High-Income Countries. *JAMA* **319,** 990 (2018).
25. OECD. *Health at a Glance 2017*. (OECD Publishing, 2017). doi:10.1787/health_glance-2017-en
26. Spear, B. B., Heath-Chiozzi, M. & Huff, J. Clinical application of pharmacogenetics. *Trends Mol. Med.* **7,** 201–204 (2001).
27. Guchet, X. Le patient « actionnable » de la médecine personnalisée. *Socio-anthropologie*

37–51 (2014). doi:10.4000/socio-anthropologie.1648

28. Haldorsen, E. M. H., M H Haldorsen, P. E. & Haldorsen, E. M. H. The right treatment to the right patient at the right time. *Occup. Environ. Med.* **60,** 235–236 (2003).
29. Pritchard, D. E. *et al.* Strategies for integrating personalized medicine into healthcare practice. *Per. Med.* **14,** 141–152 (2017).
30. Wasi, P. Human genomics: implications for health. *Southeast Asian J. Trop. Med. Public Health* **28 Suppl 2,** 19–24 (1997).
31. National Research Council (US) Committee on A Framework for Developing a New Taxonomy Of Disease. *Toward Precision Medicine*. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (National Academies Press, 2011). doi:10.17226/13284
32. Pasipoularides, A. Genomic translational research: Paving the way to individualized cardiac functional analyses and personalized cardiology. *Int. J. Cardiol.* **230,** 384–401 (2016).
33. Bonter, K., Desjardins, C., Currier, N., Pun, J. & Ashbury, F. D. Personalised medicine in Canada: a survey of adoption and practice in oncology, cardiology and family medicine. *BMJ Open* **1,** e000110–e000110 (2011).
34. Ginsburg, G. S. & Willard, H. F. Genomic and personalized medicine: foundations and applications. *Transl. Res.* **154,** 277–287 (2009).
35. Strachan, T. & Read, A. *Human Molecular Genetics*. (Garland Science, 2010). doi:0815341490
36. NHGRI Genome Sequencing Program. *DNA Sequencing Costs: Data*. (2017).
37. Oosterwijk, J. C., de Vries, J., Mourits, M. J. & de Bock, G. H. Genetic testing and familial implications in breast-ovarian cancer families. *Maturitas* **78,** 252–257 (2014).
38. McCarthy, J. J., McLeod, H. L. & Ginsburg, G. S. Genomic medicine: a decade of successes, challenges, and opportunities. *Sci. Transl. Med.* **5,** 189sr4 (2013).
39. Mestroni, L., Begay, R. L., Graw, S. L. & Taylor, M. R. G. Pharmacogenetics of heart failure. *Curr. Opin. Cardiol.* **29,** 227–34 (2014).
40. Filipski, K. K., Mechanic, L. E., Long, R. & Freedman, A. N. Pharmacogenomics in oncology care. *Front. Genet.* **5,** 73 (2014).
41. Bertier, G., Carrot-Zhang, J., Ragoussis, V. & Joly, Y. Integrating precision cancer

medicine into healthcare—policy, practice, and research challenges. *Genome Med.* **8,** 108 (2016).

42. Worst, B. C. *et al.* Next-generation personalised medicine for high-risk paediatric cancer patients – The INFORM pilot study. *Eur. J. Cancer* **65,** 91–101 (2016).
43. Harttrampf, A. C. *et al.* Molecular Screening for Cancer Treatment Optimization (MOSCATO-01) in Pediatric Patients: A Single-Institutional Prospective Molecular Stratification Trial. *Clin. Cancer Res.* **23,** 6101–6112 (2017).
44. Schork, N. J. Personalized medicine: Time for one-person trials. *Nature* **520,** 609–611 (2015).
45. Low, S.-K., Zembutsu, H. & Nakamura, Y. Breast cancer: The translation of big genomic data to cancer precision medicine. *Cancer Sci.* **109,** 497–506 (2018).
46. Subbiah, V. & Kurzrock, R. Universal Genomic Testing Needed to Win the War Against Cancer. *JAMA Oncol.* **2,** 719 (2016).
47. Marcon, A. R., Bieber, M. & Caulfield, T. Representing a "revolution": how the popular press has portrayed personalized medicine. *Genet. Med.* (2018). doi:10.1038/gim.2017.217
48. Ward, M. M. Personalized Therapeutics: A Potential Threat to Health Equity. *J. Gen. Intern. Med.* **27,** 868–870 (2012).
49. Degtiar, I. A review of international coverage and pricing strategies for personalized medicine and orphan drugs. **121,** 1240–1248 (2017).
50. Khoury, M. J., Iademarco, M. F. & Riley, W. T. Precision Public Health for the Era of Precision Medicine. *Am. J. Prev. Med.* **50,** 398–401 (2016).
51. García, M. C. *et al.* Potentially Preventable Deaths Among the Five Leading Causes of Death — United States, 2010 and 2014. *MMWR. Morb. Mortal. Wkly. Rep.* **65,** 1245–1255 (2016).
52. Feero, W. G., Wicklund, C. A. & Veenstra, D. Precision Medicine, Genome Sequencing, and Improved Population Health. *JAMA* (2018). doi:10.1001/jama.2018.2925
53. Bombard, Y. Translating personalized genomic medicine into clinical practice: evidence, values, and health policy. *Genome* **7,** 1–7 (2015).
54. Manolio, T. A. *et al.* Global implementation of genomic medicine: We are not alone. *Sci. Transl. Med.* **7,** 290ps13-290ps13 (2015).

55. Majewski, J., Schwartzentruber, J., Lalonde, E., Montpetit, A. & Jabado, N. What can exome sequencing do for you? *J. Med. Genet.* **48,** 580–589 (2011).
56. Mayer, A. N. *et al.* A timely arrival for genomic medicine. *Genet. Med.* **13,** 195–196 (2011).
57. McDonell, L. M. *et al.* The utility of exome sequencing for genetic diagnosis in a familial microcephaly epilepsy syndrome. *BMC Neurol.* **14,** 22 (2014).
58. Boycott, K. M. & Ardigó, D. Addressing challenges in the diagnosis and treatment of rare genetic diseases. *Nat. Publ. Gr.* (2017). doi:10.1038/nrd.2017.246
59. Aanensen, D. M. *et al.* Whole-Genome Sequencing for Routine Pathogen Surveillance in Public Health: a Population Snapshot of Invasive Staphylococcus aureus in Europe. *MBio* **7,** e00444-16 (2016).
60. Gardy, J. L. & Loman, N. J. Towards a genomics-informed, real-time, global pathogen surveillance system. *Nat. Rev. Genet.* **19,** 9–20 (2017).
61. Deurenberg, R. H. *et al.* Application of next generation sequencing in clinical microbiology and infection prevention. *J. Biotechnol.* **243,** 16–24 (2017).
62. Reardon, S. Fast genetic sequencing saves newborn lives. *Nature* **514,** 13–14 (2014).
63. Char, D. S. Whole-genome sequencing in critically ill infants and emerging ethical challenges. *Lancet Respir. Med.* **3,** 333–335 (2015).
64. Frankel, L. A., Pereira, S. & McGuire, A. L. Potential Psychosocial Risks of Sequencing Newborns. *Pediatrics* **137,** S24–S29 (2016).
65. Bodian, D. L. *et al.* Utility of whole-genome sequencing for detection of newborn screening disorders in a population cohort of 1,696 neonates. *Genet. Med.* **18,** 221–230 (2016).
66. Ceyhan-Birsoy, O. *et al.* A curated gene list for reporting results of newborn genomic sequencing. *Genet. Med.* **19,** 809–818 (2017).
67. Meng, L. *et al.* Use of Exome Sequencing for Infants in Intensive Care Units. *JAMA Pediatr.* **171,** e173438 (2017).
68. Borghesi, A. *et al.* Intersociety policy statement on the use of whole-exome sequencing in the critically ill newborn infant. *Ital. J. Pediatr.* **43,** 100 (2017).
69. Vassy, J. L. *et al.* The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients. *Ann. Intern. Med.* **13,** 106–15 (2017).

70. Reuter, M. S. *et al.* The Personal Genome Project Canada: findings from whole genome sequences of the inaugural 56 participants. *CMAJ* **190,** E126–E136 (2018).
71. Christensen, K. D. *et al.* Short-term costs of integrating whole-genome sequencing into primary care and cardiology settings: a pilot randomized trial. *Genet. Med.* (2018). doi:10.1038/gim.2018.35
72. Niemiec, E. & Howard, H. C. Ethical issues in consumer genome sequencing: Use of consumers' samples and data. *Appl. Transl. genomics* **8,** 23–30 (2016).
73. Niemiec, E., Borry, P., Pinxten, W. & Howard, H. C. Content Analysis of Informed Consent for Whole Genome Sequencing Offered by Direct-to-Consumer Genetic Testing Companies. *Hum. Mutat.* **37,** 1248–1256 (2016).
74. Nelson, S. C. & Fullerton, S. M. "Bridge to the Literature"? Third-Party Genetic Interpretation Tools and the Views of Tool Developers. *J. Genet. Couns.* (2018). doi:10.1007/s10897-018-0217-9
75. Tandy-Connor, S. *et al.* False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet. Med.* (2018). doi:10.1038/gim.2018.38
76. Philippakis, A. A. *et al.* The Matchmaker Exchange: a platform for rare disease gene discovery. *Hum. Mutat.* **36,** 915–21 (2015).
77. Chérot, E. *et al.* Using medical exome sequencing to identify the causes of neurodevelopmental disorders: Experience of 2 clinical units and 216 patients. *Clin. Genet.* **93,** 567–576 (2018).
78. Sawyer, S. L. *et al.* Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: Time to address gaps in care. *Clin. Genet.* 275–284 (2015). doi:10.1111/cge.12654
79. Lazaridis, K. N. *et al.* Outcome of Whole Exome Sequencing for Diagnostic Odyssey Cases of an Individualized Medicine Clinic. *Mayo Clin. Proc.* **91,** 297–307 (2016).
80. Córdoba, M. *et al.* Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach. *PLoS One* **13,** e0191228 (2018).
81. Thevenon, J. *et al.* Diagnostic odyssey in severe neurodevelopmental disorders: Toward clinical whole-exome sequencing as a first-line diagnostic test. *Clin. Genet.* **89,** 700–707 (2016).

82. Posey, J. E. *et al.* Molecular diagnostic experience of whole-exome sequencing in adult patients. *Genet. Med.* **18,** 678–685 (2016).
83. Alfares, A. *et al.* A multicenter clinical exome study in unselected cohorts from a consanguineous population of Saudi Arabia demonstrated a high diagnostic yield. *Mol. Genet. Metab.* **121,** 91–95 (2017).
84. Lee, H. *et al.* Clinical Exome Sequencing for Genetic Identification of Rare Mendelian Disorders. *JAMA* **312,** 1880 (2014).
85. Eldomery, M. K. *et al.* Lessons learned from additional research analyses of unsolved clinical exome cases. *Genome Med.* **9,** 26 (2017).
86. Ewans, L. J. *et al.* Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. *Genet. Med.* (2018). doi:10.1038/gim.2018.39
87. Saudi Mendeliome Group. Comprehensive gene panels provide advantages over clinical exome sequencing for Mendelian diseases. *Genome Biol.* **16,** 134 (2015).
88. Schwarze, K., Buchanan, J., Taylor, J. C. & Wordsworth, S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet. Med.* (2018). doi:10.1038/gim.2017.247
89. Monroe, G. R. *et al.* Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability. *Genet. Med.* **18,** 949–956 (2016).
90. Trujillano, D. *et al.* Clinical exome sequencing: results from 2819 samples reflecting 1000 families. *Eur. J. Hum. Genet.* **25,** 176–182 (2017).
91. Thuriot, F. *et al.* Clinical validity of phenotype-driven analysis software PhenoVar as a diagnostic aid for clinical geneticists in the interpretation of whole-exome sequencing data. *Genet Med* (2018). doi:10.1038/gim.2017.239
92. Gauthier-Vasserot, A. *et al.* Application of whole-exome sequencing to unravel the molecular basis of undiagnosed syndromic congenital neutropenia with intellectual disability. *Am. J. Med. Genet. Part A* **173,** 62–71 (2017).
93. Srivastava, S. *et al.* Clinical whole exome sequencing in child neurology practice. *Ann. Neurol.* **76,** 473–483 (2014).
94. Bourchany, A. *et al.* Reducing diagnostic turnaround times of exome sequencing for

families requiring timely diagnoses. *Eur. J. Med. Genet.* **60,** 595–604 (2017).

95. Long, P., Evans, J. & Olson, T. Diagnostic Yield of Whole Exome Sequencing in Pediatric Dilated Cardiomyopathy. *J. Cardiovasc. Dev. Dis.* **4,** 11 (2017).
96. Cohen, L. *et al.* [UTILIZATION OF WHOLE EXOME SEQUENCING IN DIAGNOSTICS OF GENETIC DISEASE: RABIN MEDICAL CENTER'S EXPERIENCE]. *Harefuah* **156,** 212–216 (2017).
97. Tan, T. Y. *et al.* Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children With Suspected Monogenic Conditions. *JAMA Pediatr.* **171,** 855 (2017).
98. Stark, Z. *et al.* A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet. Med.* **18,** 1090–1096 (2016).
99. Yavarna, T. *et al.* High diagnostic yield of clinical exome sequencing in Middle Eastern patients with Mendelian disorders. *Hum. Genet.* **134,** 967–980 (2015).
100. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2018. *CA. Cancer J. Clin.* **68,** 7–30 (2018).
101. Lefebvre, C. *et al.* Mutational Profile of Metastatic Breast Cancers: A Retrospective Analysis. *PLoS Med.* **13,** 1–18 (2016).
102. Delattre, O. & Bult, C. J. Editorial overview: Characterizing the cancer genome: mechanistic insights and translational opportunities. *Curr. Opin. Genet. Dev.* **42,** 78–80 (2017).
103. Banan, R. & Hartmann, C. The new WHO 2016 classification of brain tumors—what neurosurgeons need to know. *Acta Neurochir. (Wien).* **159,** 403–418 (2017).
104. Jones, C. *et al.* Pediatric high-grade glioma: biologically and clinically in need of new thinking. *Neuro. Oncol.* **19,** now101 (2016).
105. Müllauer, L. Next generation sequencing: clinical applications in solid tumours. *Memo* **10,** 244–247 (2017).
106. West, H. (Jack). No Solid Evidence, Only Hollow Argument for Universal Tumor Sequencing. *JAMA Oncol.* **2,** 717 (2016).
107. Massard, C. *et al.* High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial. *Cancer Discov.* **7,** 586–595

(2017).

108. Mody, R. J. *et al.* Integrative Clinical Sequencing in the Management of Refractory or Relapsed Cancer in Youth. *JAMA* **314,** 913 (2015).
109. Harris, M. H. *et al.* Multicenter Feasibility Study of Tumor Molecular Profiling to Inform Therapeutic Decisions in Advanced Pediatric Solid Tumors. *JAMA Oncol.* **2,** 608 (2016).
110. Parsons, D. W. *et al.* Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. *JAMA Oncol.* (2016). doi:10.1001/jamaoncol.2015.5699
111. Pincez, T. *et al.* Feasibility and clinical integration of molecular profiling for target identification in pediatric solid tumors. *Pediatr. Blood Cancer* **64,** e26365 (2017).
112. Weymann, D. *et al.* The cost and cost trajectory of whole-genome analysis guiding treatment of patients with advanced cancers. *Mol. Genet. Genomic Med.* **5,** 251–260 (2017).
113. Laskin, J. *et al.* Lessons learned from the application of whole-genome analysis to the treatment of patients with advanced cancers. *Mol. Case Stud.* **1,** a000570 (2015).
114. Robinson, D. R. *et al.* Integrative clinical genomics of metastatic cancer. *Nature* **548,** 297–303 (2017).
115. Dearing, K. R. & Weiss, G. J. Translating next-generation sequencing from clinical trials to clinical practice for the treatment of advanced cancers. *Per. Med.* **12,** 155–162 (2015).
116. Allin, S. & Rudoler, D. *The Canadian Health Care System*. (2017).
117. Labrie, Y. & Boyer, M. The private sector within a public health care system: the French example. *Montr. Econ. Ist. Econ. Note* **Health Car,** (2008).
118. Baron, E. Liberté, égalité, fraternité…santé. *Lancet* **387,** 2179–2181 (2016).
119. Isabelle Durand-Zaleski. *The French Health Care System*. (2017).
120. The Economist Intelligence Unit. France: With a high-quality, accessible and affordable healthcare system, the focus is now on cost containment and reducing the country's large healthcare deficit. *Value-based Healthc. A Glob. Assess.* (2016).
121. Tabori, U. *et al.* Clinical management and tumor surveillance recommendations of inherited mismatch repair deficiency in childhood. *Clin. Cancer Res.* **23,** e32–e37 (2017).
122. Koeppel, F. *et al.* Whole exome sequencing for determination of tumor mutation load in liquid biopsy from advanced cancer patients. *PLoS One* **12,** e0188174 (2017).

123. Forrest, S. J., Geoerger, B. & Janeway, K. A. Precision medicine in pediatric oncology. *Curr. Opin. Pediatr.* 1 (2017). doi:10.1097/MOP.0000000000000570
124. Bruel, A.-L. *et al.* Fifteen years of research on oral–facial–digital syndromes: from 1 to 16 causal genes. *J. Med. Genet.* **54,** 371–380 (2017).
125. Postel-Vinay, S. *et al.* Seeking the driver in tumours with apparent normal molecular profile on comparative genomic hybridization and targeted gene panel sequencing: what is the added value of whole exome sequencing? *Ann. Oncol.* **27,** 344–352 (2016).
126. Abaji, R. *et al.* Whole-exome sequencing identified genetic risk factors for asparaginase-related complications in childhood all patients. *Oncotarget* **8,** 43752–43767 (2015).
127. Spinella, J.-F. *et al.* SNooPer: a machine learning-based method for somatic variant identification from low-pass next-generation sequencing. *BMC Genomics* **17,** 912 (2016).
128. Dieci, M. V. *et al.* Whole exome sequencing of rare aggressive breast cancer histologies. *Breast Cancer Res. Treat.* **156,** 21–32 (2016).
129. Lévy, Y. *France Médecine Génomique 2025*. (2016).
130. Gaff, C. L. *et al.* Preparing for genomic medicine: a real world demonstration of health system change. *npj Genomic Med.* **2,** 16 (2017).
131. Ashtiani, S., Makela, N., Carrion, P. & Austin, J. Parents' experiences of receiving their child's genetic diagnosis: A qualitative study to inform clinical genetics practice. *Am. J. Med. Genet. Part A* **164,** 1496–1502 (2014).
132. Townsend, A. *et al.* 'I want to know what's in Pandora's box': Comparing stakeholder perspectives on incidental findings in clinical whole genomic sequencing. *Am. J. Med. Genet. Part A* **158 A,** 2519–2525 (2012).
133. Levenseller, B. L. *et al.* Stakeholders' Opinions on the Implementation of Pediatric Whole Exome Sequencing: Implications for Informed Consent. *J. Genet. Couns.* **23,** 552–565 (2014).
134. Lohn, Z., Adam, S., Birch, P., Townsend, A. & Friedman, J. Genetics professionals' perspectives on reporting incidental findings from clinical genome-wide sequencing. *Am. J. Med. Genet. Part A* **161,** 542–549 (2013).
135. Machini, K., Douglas, J., Braxton, A., Tsipis, J. & Kramer, K. Genetic Counselors' Views and Experiences with the Clinical Integration of Genome Sequencing. *J. Genet. Couns.* **23,** 496–505 (2014).

136. Lazarus, J. Doctors (Cautiously) Onboard. *GeneWatch* (2012).
137. Raghavan, S. & Vassy, J. L. Do physicians think genomic medicine will be useful for patient care? *Per. Med.* **11,** 424–433 (2014).
138. Phillips, K. A., Liang, S.-Y. & Van Bebber, S. Challenges to the translation of genomic information into clinical practice and health policy: Utilization, preferences and economic value. *Curr. Opin. Mol. Ther.* **10,** 260–6 (2008).
139. American Academy of Pediatrics, Committee on Bioethics, Committee on Genetics, the American College of Medical Genetics and Genomics Social Ethical and Legal Issues Committee & American Academy of Pediatrics. Ethical and Policy Issues in Genetic Testing and Screening of Children. *Pediatrics* **131,** 620–622 (2013).
140. Wade, C. H., Tarini, B. A. & Wilfond, B. S. Growing Up in the Genomic Era: Implications of Whole-Genome Sequencing for Children, Families, and Pediatric Practice. *Annu. Rev. Genomics Hum. Genet.* **14,** 535–555 (2013).
141. Erika Check Hayden, Hayden, E. C. & Erika Check Hayden. Privacy protections: The genome hacker. *Nature* **497,** 1–3 (2013).
142. Ormond, K. E. & Cho, M. K. Translating personalized medicine using new genetic technologies in clinical practice: the ethical issues. *Per. Med.* **11,** 211–222 (2014).
143. Pinxten, W. & Howard, H. C. Ethical issues raised by whole genome sequencing. *Best Pract. Res. Clin. Gastroenterol.* **28,** 269–279 (2014).
144. Kaname, T., Yanagi, K. & Naritomi, K. A commentary on the promise of whole-exome sequencing in medical genetics. *J. Hum. Genet.* **59,** 117–8 (2014).
145. Lyon, G. J. & O'Rawe, J. Human genetics and clinical aspects of neurodevelopmental disorders. in *The Genetics of Neurodevelopmental Disorders* (ed. Mitchell, K. .) 289–317 (John Wiley & Sons, Inc., 2015).
146. Hart, S. N. *et al.* SoftSearch: integration of multiple sequence features to identify breakpoints of structural variations. *PLoS One* **8,** e83356 (2013).
147. Lonigro, R. J. *et al.* Detection of Somatic Copy Number Alterations in Cancer Using Targeted Exome Capture Sequencing. *Neoplasia* **13,** 1019-IN21 (2011).
148. Liang, D. *et al.* Copy number variation sequencing for comprehensive diagnosis of chromosome disease syndromes. *J. Mol. Diagn.* **16,** 519–26 (2014).
149. Samarakoon, P. S. *et al.* Identification of copy number variants from exome sequence

data. *BMC Genomics* **15,** 661 (2014).

150. Sastre, L. Exome sequencing: what clinicians need to know. *Adv. Genomics Genet.* **4,** 15–27 (2014).
151. Jayadev, S., Smith, C. O. & Bird, T. D. Neurogenetics: Five new things. *Neurol. Clin. Pract.* **1,** 41–48 (2011).
152. Jackson, D. B. & Sood, A. K. Personalized cancer medicine--advances and socio-economic challenges. *Nat. Rev. Clin. Oncol.* **8,** 735–41 (2011).
153. Jamal, S. M. *et al.* Practices and policies of clinical exome sequencing providers: analysis and implications. *Am. J. Med. Genet. A* **161A,** 935–50 (2013).
154. Pokorska-Bocci, A., Kroese, M., Sagoo, G. S., Hall, A. & Burton, H. Personalised medicine in the UK: challenges of implementation and impact on healthcare system. *Genome Med.* **6,** 28 (2014).
155. DeVita, V. T., Eggermont, A. M. M., Hellman, S. & Kerr, D. J. Clinical cancer research: the past, present and the future. *Nat. Rev. Clin. Oncol.* **11,** 663–669 (2014).
156. Johansen Taber, K. A., Dickinson, B. D. & Wilson, M. The promise and challenges of next-generation genome sequencing for clinical care. *JAMA Intern. Med.* **174,** 275–80 (2014).
157. McGuire, A. L., Knoppers, B. M., Zawati, M. H. & Clayton, E. W. Can I be sued for that? Liability risk and the disclosure of clinically significant genetic research findings. *Genome Res.* **24,** 719–23 (2014).
158. Green, R. C. *et al.* ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* **15,** 565–574 (2013).
159. Allyse, M. & Michie, M. Not-so-incidental findings: the ACMG recommendations on the reporting of incidental findings in clinical whole genome and whole exome sequencing. *Trends Biotechnol.* **31,** 439–41 (2013).
160. Townsend, A., Adam, S., Birch, P. H. & Friedman, J. M. Paternalism and the ACMG recommendations on genomic incidental findings: patients seen but not heard. *Genet. Med.* **15,** 751–752 (2013).
161. McCormick, J. B. *et al.* Genomic medicine and incidental findings: balancing actionability and patient autonomy. *Mayo Clin. Proc.* **89,** 718–21 (2014).
162. Vayena, E. & Tasioulas, J. Genetic incidental findings: autonomy regained? *Genet. Med.*

15, 868–870 (2013).

163. ACMG Board of Directors. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genet. Med.* **17,** 68–69 (2015).
164. Hehir-Kwa, J. Y. *et al.* Towards a European consensus for reporting incidental findings during clinical NGS testing. *Eur. J. Hum. Genet.* (2015). doi:10.1038/ejhg.2015.111
165. Boycott, K. *et al.* The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. *J. Med. Genet.* **52,** 431–437 (2015).
166. Knobloch, K., Yoon, U. & Vogt, P. M. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. *J. Craniomaxillofac. Surg.* **39,** 91–92 (2011).
167. Petticrew, M. & Roberts, H. *Systematic Reviews in the Social Sciences: A Practical Guide*. (Blackwell Publishing, 2006). doi:10.1027/1016-9040.11.3.244
168. Elo, S. & Kyngäs, H. The qualitative content analysis process. *J. Adv. Nurs.* **62,** 107–15 (2008).
169. Downe-Wamboldt, B. Content analysis: Method, applications, and issues. *Health Care Women Int.* **13,** 313–321 (1992).
170. Vorderstrasse, A. a., Hammer, M. J. & Dungan, J. R. Nursing implications of personalized and precision medicine. *Semin. Oncol. Nurs.* **30,** 130–136 (2014).
171. Williams, E. S. & Hegde, M. Implementing Genomic Medicine in Pathology. *Adv. Anat. Pathol.* **20,** 238–244 (2013).
172. Merrill, S. L., Vaidya, A. & Pyeritz, R. E. Ethical Challenges of the Use of Whole Exome Sequencing in the Clinic. *World J. Pediatr. Congenit. Hear. Surg.* **4,** 58–61 (2013).
173. Girolami, F. *et al.* Novel -Actinin 2 Variant Associated With Familial Hypertrophic Cardiomyopathy and Juvenile Atrial Arrhythmias: A Massively Parallel Sequencing Study. *Circ. Cardiovasc. Genet.* **7,** 741–750 (2014).
174. Takeichi, T. *et al.* Whole-exome sequencing improves mutation detection in a diagnostic epidermolysis bullosa laboratory. *Br. J. Dermatol.* **172,** 94–100 (2015).
175. Carss, K. J. *et al.* Exome sequencing improves genetic diagnosis of structural fetal abnormalities revealed by ultrasound. *Hum. Mol. Genet.* **23,** 3269–3277 (2014).

176. Need, A. C. *et al.* Clinical application of exome sequencing in undiagnosed genetic conditions. *J. Med. Genet.* **49,** 353–61 (2012).
177. Coonrod, E. M., Durtschi, J. D., Margraf, R. L. & Voelkerding, K. V. Developing Genome and Exome Sequencing for Candidate Gene Identification in Inherited Disorders: An Integrated Technical and Bioinformatics Approach. *Arch. Pathol. Lab. Med.* **137,** 415–433 (2013).
178. Lacroix, L., Boichard, A., André, F. & Soria, J.-C. Genomes in the clinic: the Gustave Roussy Cancer Center experience. *Curr. Opin. Genet. Dev.* **24,** 99–106 (2014).
179. Levenson, D. Whole-exome sequencing emerges as clinical diagnostic tool. *Am. J. Med. Genet. Part A* **164,** ix–x (2014).
180. Lazaridis, K. N. *et al.* Implementing individualized medicine into the medical practice. *Am. J. Med. Genet. C. Semin. Med. Genet.* **166C,** 15–23 (2014).
181. van Zelst-Stams, W. A., Scheffer, H. & Veltman, J. A. Clinical exome sequencing in daily practice: 1,000 patients and beyond. *Genome Med.* **6,** 2 (2014).
182. Jacob, H. J. *et al.* Genomics in Clinical Practice: Lessons from the Front Lines. *Sci. Transl. Med.* **5,** 194cm5 (2013).
183. Malhotra, A., Levine, S. & Allingham-Hawkins, D. Whole exome sequencing for cancer – is there evidence of clinical utility? *Adv. Genomics Genet.* **Volume 4,** 115 (2014).
184. Chang, F. & Li, M. M. Clinical application of amplicon-based next-generation sequencing in cancer. *Cancer Genet.* **206,** 413–419 (2013).
185. Boycott, K. M., Vanstone, M. R., Bulman, D. E. & MacKenzie, A. E. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. *Nat. Rev. Genet.* **14,** 681–691 (2013).
186. Lee, H. & Nelson, S. F. Rethinking clinical practice : clinical implementation of exome sequencing E ditorial. *Per. Med.* **9,** 785–787 (2012).
187. Bacher, U., Kohlmann, A. & Haferlach, T. Mutational profiling in patients with MDS: ready for every-day use in the clinic? *Best Pract. Res. Clin. Haematol.* **28,** 32–42 (2015).
188. Arts, H. H. & Knoers, N. V. A. M. Current insights into renal ciliopathies: what can genetics teach us? *Pediatr. Nephrol.* **28,** 863–874 (2013).
189. Berg, J. S. *et al.* Next generation massively parallel sequencing of targeted exomes to identify genetic mutations in primary ciliary dyskinesia: Implications for application to

clinical testing. *Genet. Med.* **13,** 218–229 (2011).

190. Sutton, A. L. M. & Robin, N. H. Clinical application of whole exome sequencing: not (yet) ready for primetime. *Curr. Opin. Pediatr.* **24,** 663–4 (2012).
191. Xue, Y., Ankala, A., Wilcox, W. R. & Hegde, M. R. Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. *Genet. Med.* **17,** 444–451 (2015).
192. Klein, H.-G., Bauer, P. & Hambuch, T. Whole genome sequencing (WGS), whole exome sequencing (WES) and clinical exome sequencing (CES) in patient care. *LaboratoriumsMedizin* **38,** 221–230 (2014).
193. Graubert, T. & Stone, R. AML genomics for the clinician. *Semin. Hematol.* **51,** 322–9 (2014).
194. Newman, W. & Black, G. Delivery of a Clinical Genomics Service. *Genes (Basel).* **5,** 1001–1017 (2014).
195. Sisodiya, S. M. Genetic screening and diagnosis in epilepsy? *Curr. Opin. Neurol.* **28,** 136–142 (2015).
196. Marian, A. J. Sequencing your genome: what does it mean? *Methodist Debakey Cardiovasc. J.* **10,** 3–6 (2014).
197. Gillespie, R. L., Hall, G. & Black, G. C. Genetic testing for inherited ocular disease: delivering on the promise at last? *Clin. Experiment. Ophthalmol.* **42,** 65–77 (2014).
198. Sankaran, V. G. & Gallagher, P. G. Applications of high-throughput DNA sequencing to benign hematology. *Blood* **122,** 3575–3582 (2013).
199. Jongbloed, J. D., Pósafalvi, A., Kerstjens-Frederikse, W. S., Sinke, R. J. & van Tintelen, J. P. New clinical molecular diagnostic methods for congenital and inherited heart disease. *Expert Opin. Med. Diagn.* **5,** 9–24 (2011).
200. Lin, X. *et al.* Applications of targeted gene capture and next-generation sequencing technologies in studies of human deafness and other genetic disabilities. *Hear. Res.* **288,** 67–76 (2012).
201. Topper, S., Ober, C. & Das, S. Exome sequencing and the genetics of intellectual disability. *Clin. Genet.* **80,** 117–26 (2011).
202. Desai, A. N. & Jere, A. Next-generation sequencing: ready for the clinics? *Clin. Genet.* **81,** 503–10 (2012).

203. Thomas, F., Desmedt, C., Aftimos, P. & Awada, A. Impact of tumor sequencing on the use of anticancer drugs. *Curr. Opin. Oncol.* **26,** 347–56 (2014).
204. Rossor, A. M., Polke, J. M., Houlden, H. & Reilly, M. M. Clinical implications of genetic advances in Charcot-Marie-Tooth disease. *Nat. Rev. Neurol.* **9,** 562–71 (2013).
205. Rabbani, B., Tekin, M. & Mahdieh, N. The promise of whole-exome sequencing in medical genetics. *J. Hum. Genet.* **59,** 5–15 (2014).
206. Ream, M. A. & Mikati, M. A. Clinical utility of genetic testing in pediatric drug-resistant epilepsy: A pilot study. *Epilepsy Behav.* **37,** 241–248 (2014).
207. Nigro, V. & Piluso, G. Next generation sequencing (NGS) strategies for the genetic testing of myopathies. *Acta Myol.* **31,** 196–200 (2012).
208. Shkedi-Rafid, S., Dheensa, S., Crawford, G., Fenwick, A. & Lucassen, A. Defining and managing incidental findings in genetic and genomic practice. *J. Med. Genet.* **51,** 715–23 (2014).
209. Knoppers, B. M., Zawati, M. H. & Sénécal, K. Return of genetic testing results in the era of whole-genome sequencing. *Nat. Rev. Genet.* **16,** 553–559 (2015).
210. Lyon, G. J. & Wang, K. Identifying disease mutations in genomic medicine settings: current challenges and how to accelerate progress. *Genome Med.* **4,** 58 (2012).
211. Gecz, J. & Corbett, M. Developmental disorders: deciphering exomes on a grand scale. *Lancet (London, England)* **385,** 1266–7 (2015).
212. Zanolli, M. T., Khetan, V., Dotan, G., Pizzi, L. & Levin, A. V. Should patients with ocular genetic disorders have genetic testing? *Curr. Opin. Ophthalmol.* **25,** 359–65 (2014).
213. Gallego, C. J. *et al.* Comparative effectiveness of next generation genomic sequencing for disease diagnosis: design of a randomized controlled trial in patients with colorectal cancer/polyposis syndromes. *Contemp. Clin. Trials* **39,** 1–8 (2014).
214. Jiang, Y.-H. *et al.* Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. *Crit. Rev. Clin. Lab. Sci.* **51,** 249–62 (2014).
215. Gibson, J., Young, S., Leng, B., Zreik, R. & Rao, A. Molecular diagnostic testing of cytology specimens: current applications and future considerations. *J. Am. Soc. Cytopathol.* **3,** 280–294 (2014).
216. Lohmann, K. & Klein, C. Next generation sequencing and the future of genetic diagnosis. *Neurotherapeutics* **11,** 699–707 (2014).

217. Goldberg, A., Curtis, C. L. & Kleim, J. A. Linking genes to neurological clinical practice: the genomic basis for neurorehabilitation. *J. Neurol. Phys. Ther.* **39,** 52–61 (2015).
218. Glade Bender, J., Verma, A. & Schiffman, J. D. Translating genomic discoveries to the clinic in pediatric oncology. *Curr. Opin. Pediatr.* **27,** 34–43 (2015).
219. Lubitz, S. A. & Ellinor, P. T. Next-generation sequencing for the diagnosis of cardiac arrhythmia syndromes. *Heart Rhythm* **12,** 1062–70 (2015).
220. Fridman, V. & Murphy, S. M. The spectrum of axonopathies: from CMT2 to HSP. *Neurology* **83,** 580–1 (2014).
221. Tang, Y., Stahl-Herz, J. & Sampson, B. A. Molecular diagnostics of cardiovascular diseases in sudden unexplained death. *Cardiovasc. Pathol.* **23,** 1–4 (2014).
222. Iacobazzi, V., Infantino, V., Castegna, A. & Andria, G. Hyperhomocysteinemia: related genetic diseases and congenital defects, abnormal DNA methylation and newborn screening issues. *Mol. Genet. Metab.* **113,** 27–33 (2014).
223. Liu, Z.-J. *et al.* Identify mutation in amyotrophic lateral sclerosis cases using HaloPlex target enrichment system. *Neurobiol. Aging* **35,** 2881.e11-5 (2014).
224. Sanchez, M., Levine, R. L. & Rampal, R. Integrating genomics into prognostic models for AML. *Semin. Hematol.* **51,** 298–305 (2014).
225. Smith, A., Boycott, K. M. & Jarinova, O. Lake Louise Mutation Detection Meeting 2013: Clinical Translation of Next-Generation Sequencing Requires Optimization of Workflows and Interpretation of Variants. *Hum. Mutat.* **35,** 265–269 (2014).
226. Dacic, S. M. D. P. & Nikiforova, M. N. M. D. Present and Future Molecular Testing of Lung Carcinoma. *Adv. Anat. Pathol.* **21,** 94–99 (2014).
227. Babkina, N. & Graham, J. M. New genetic testing in prenatal diagnosis. *Semin. Fetal Neonatal Med.* **19,** 214–219 (2014).
228. Beckmann, J. S. Can We Afford to Sequence Every Newborn Baby's Genome? *Hum. Mutat.* **36,** 283–286 (2015).
229. Williams, J. K., Cashion, A. K. & Veenstra, D. L. Challenges in evaluating next-generation sequence data for clinical decisions. *Nurs. Outlook* **63,** 48–50 (2015).
230. Berg, J. S. Genome-Scale Sequencing in Clinical Care. *JAMA* **312,** 1865 (2014).
231. Shashi, V. *et al.* Practical considerations in the clinical application of whole-exome sequencing. *Clin. Genet.* **89,** 173–181 (2016).

232. Atwal, P. S. *et al.* Clinical whole-exome sequencing: are we there yet? *Genet. Med.* **16,** 717–719 (2014).
233. Kamalakaran, S. *et al.* Translating next generation sequencing to practice: Opportunities and necessary steps. *Mol. Oncol.* **7,** 743–755 (2013).
234. Matthijs, G. *et al.* Guidelines for diagnostic next-generation sequencing. *Eur. J. Hum. Genet.* **24,** 2–5 (2016).
235. Richards, S. *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* **17,** 405–423 (2015).
236. Sabatini, L. M. *et al.* Genomic Sequencing Procedure Microcosting Analysis and Health Economic Cost-Impact Analysis. *J. Mol. Diagnostics* **18,** 319–328 (2016).
237. Amendola, L. M. *et al.* Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. *Am. J. Hum. Genet.* **98,** 1067–1076 (2016).
238. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet. Med.* **17,** 505–507 (2015).
239. Vrijenhoek, T. *et al.* Next-generation sequencing-based genome diagnostics across clinical genetics centers: implementation choices and their effects. *Eur. J. Hum. Genet.* **23,** 1142–1150 (2015).
240. Feinberg, J. The Child's Right to an Open Future. in *Whose child? Children's rights, parental authority, and state power. Totowa, NJ: Rowman & Littlefield. W. Aiken and H. LaFollette (eds.).* 124–153 (1980).
241. Millum, J. The foundation of the child's right to an open future. *J. Soc. Philos.* **45,** 522–538 (2014).
242. Borry, P., Shabani, M. & Howard, H. C. Is There a Right Time to Know? The Right Not to Know and Genetic Testing in Children. *J. Law. Med. Ethics* **42,** 19–27 (2014).
243. Bredenoord, A. L., de Vries, M. C. & van Delden, J. J. M. Next-generation sequencing: does the next generation still have a right to an open future? *Nat. Rev. Genet.* **14,** 306–306 (2013).
244. Sabatello, M., Dollard, E. K. & Appelbaum, P. S. Raising Genomic Citizens: Adolescents

and the Return of Secondary Genomic Findings. *J Law Med Ethics* **44,** 292–308 (2016).

245. Chen, S. C. & Wasserman, D. T. A Framework for Unrestricted Prenatal Whole-Genome Sequencing: Respecting and Enhancing the Autonomy of Prospective Parents. doi:10.1080/15265161.2016.1251632
246. Koboldt, D. C., Steinberg, K. M., Larson, D. E., Wilson, R. K. & Mardis, E. R. The next-generation sequencing revolution and its impact on genomics. *Cell* **155,** 27–38 (2013).
247. Botkin, J. R. *et al.* Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *Am. J. Hum. Genet.* **97,** 6–21 (2015).
248. Katsanis, S. H. & Katsanis, N. Molecular genetic testing and the future of clinical genomics. *Nat. Rev. Genet.* **14,** 415–426 (2013).
249. Biesecker, L. G., Green, R. C., Phimister, E. G., Biesecker, L. G. & Green, R. C. Diagnostic Clinical Genome and Exome Sequencing. *N. Engl. J. Med.* **370,** 2418–2425 (2014).
250. Russell, M. *et al.* How to effectively utilize genetic testing in the care of children with cardiomyopathies. *Prog. Pediatr. Cardiol.* **39,** 3–11 (2015).
251. Sayson, B. *et al.* Retrospective analysis supports algorithm as efficient diagnostic approach to treatable intellectual developmental disabilities. *Mol. Genet. Metab.* **115,** 1–9 (2015).
252. Soden, S. E. *et al.* Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci. Transl. Med.* **6,** 265ra168 (2014).
253. Tetreault, M., Bareke, E., Nadaf, J., Alirezaie, N. & Majewski, J. Whole-exome sequencing as a diagnostic tool: current challenges and future opportunities. *Expert Rev. Mol. Diagn.* **15,** 749–60 (2015).
254. Huser, V., Sincan, M. & Cimino, J. J. Developing genomic knowledge bases and databases to support clinical management: current perspectives. *Pharmgenomics. Pers. Med.* **7,** 275–83 (2014).
255. Grody, W. W., Thompson, B. H. & Hudgins, L. Whole-Exome/Genome Sequencing and Genomics. *Pediatrics* **132,** S211–S215 (2013).
256. Vora, N. L. & O'Brien, B. M. Noninvasive prenatal testing for microdeletion syndromes and expanded trisomies: proceed with caution. *Obstet. Gynecol.* **123,** 1097–9 (2014).

257. O'Donnell-Luria, A. H. & Miller, D. T. A Clinician's perspective on clinical exome sequencing. *Hum. Genet.* (2016). doi:10.1007/s00439-016-1662-x
258. Neveling, K. *et al.* A Post-Hoc Comparison of the Utility of Sanger Sequencing and Exome Sequencing for the Diagnosis of Heterogeneous Diseases. *Hum. Mutat.* **34,** 1721–1726 (2013).
259. Arboleda, V. *et al.* Targeted massively parallel sequencing provides comprehensive genetic diagnosis for patients with disorders of sex development. *Clin. Genet.* **83,** 35–43 (2013).
260. Vasta, V., Merritt II, J. L., Saneto, R. P. & Hahn, S. H. Next-generation sequencing for mitochondrial diseases: A wide diagnostic spectrum. *Pediatr. Int.* **54,** 585–601 (2012).
261. Holtzman, N. A. Predictive Genetic Testing: From Basic Research to Clinical Practice. *Science (80-.).* **278,** 602–605 (1997).
262. Biesecker, L. G. & Biesecker, B. B. An approach to pediatric exome and genome sequencing. *Curr. Opin. Pediatr.* **26,** 639–645 (2014).
263. Gonzalez-Garay, M. L., McGuire, A. L., Pereira, S. & Caskey, C. T. Personalized genomic disease risk of volunteers. *Proc. Natl. Acad. Sci.* **110,** 16957–16962 (2013).
264. Gomez-Lobo, V. Multidisciplinary care for individuals with disorders of sex development. *Curr. Opin. Obstet. Gynecol.* **26,** 366–371 (2014).
265. Bennett, N. C. & Farah, C. S. Next-generation sequencing in clinical oncology: next steps towards clinical validation. *Cancers (Basel).* **6,** 2296–312 (2014).
266. ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet. Med.* **14,** 759–761 (2012).
267. ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. *Genet. Med.* **15,** 748–749 (2013).
268. van El, C. G. *et al.* Whole-genome sequencing in health care: recommendations of the European Society of Human Genetics. *Eur. J. Hum. Genet.* **21,** 580–4 (2013).
269. Gargis, A. S. *et al.* Good laboratory practice for clinical next-generation sequencing informatics pipelines. *Nat. Biotechnol.* **33,** 689–93 (2015).
270. Miller, N. A. *et al.* A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases. *Genome Med.* **7,** 100 (2015).
271. Warr, A. *et al.* Exome Sequencing: Current and Future Perspectives. *G3-*

Genes|Genomes|Genetics **5,** 1543–1550 (2015).

272. Aziz, N. *et al.* College of American Pathologists' Laboratory Standards for Next-Generation Sequencing Clinical Tests. *Arch. Pathol. Lab. Med.* **139,** 481–493 (2015).
273. Rehm, H. L. *et al.* ACMG clinical laboratory standards for next-generation sequencing. *Genet. Med.* **15,** 733–747 (2013).
274. Sénécal, K., Vears, D. F., Bertier, G., Knoppers, B. M. & Borry, P. Genome-based newborn screening: a conceptual analysis of the best interests of the child standard. *Per. Med.* **12,** 439–441 (2015).
275. Rahimzadeh, V., Avard, D., Sénécal, K., Knoppers, B. M. & Sinnett, D. To disclose, or not to disclose? Context matters. *Eur. J. Hum. Genet.* **23,** 279–284 (2015).
276. The Global Alliance for Genomics and Health *et al.* A federated ecosystem for sharing genomic, clinical data. *Science (80-.).* **352,** 1278–80 (2016).
277. Lu, C. Y. *et al.* A proposed approach to accelerate evidence generation for genomic-based technologies in the context of a learning health system. *Nat. Publ. Gr.* (2017). doi:10.1038/gim.2017.122
278. Stake, R. E. *Chapter 14 - Case Studies*. *Handbook of Qualitative Research* (SAGE Publications, 1994). doi:10.1258/096214400320575624
279. Yin, R. K. *Applied Social Research Methods Series. 4th ed. Vol. 5, Case Study Research: Design and Methods*. (SAGE Publications, 2008).
280. Baxter, P. & Jack, S. Qualitative Case Study Methodology: Study Design and Implementation for Novice Researchers. *Qual. Rep.* **13,** 544–559 (2008).
281. Lejeune, C. *Manuel d'analyse Qualitative: Analyser Sans Compter Ni Classer*. (De Boeck Supérieur, 2014).
282. Eisenhardt, K. M. Building Theories from Case Study Research. *Acad. Manag. Rev.* **14,** 532–550 (1989).
283. Alison Hall, Finnegan, T. & Alberg, C. *Realising genomics in clinical practice*. (2014).
284. National Human Genome Research Institute (NHGRI). DNA Sequencing Costs. Available at: http://www.genome.gov/sequencingcosts/. (Accessed: 11th March 2015)
285. Steinbock, L. J. & Radenovic, a. The emergence of nanopores in next-generation sequencing. *Nanotechnology* **26,** 074003 (2015).
286. Hartley, T. *et al.* Whole-exome sequencing is a valuable diagnostic tool for inherited

peripheral neuropathies: Outcomes from a cohort of 50 families. *Clin. Genet.* **93,** 301–309 (2018).

287. Ramkissoon, S. H. *et al.* Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: precision medicine analysis of 203 pediatric brain tumors. *Neuro. Oncol.* now294 (2017). doi:10.1093/neuonc/now294
288. Hintzsche, J. *et al.* IMPACT: a whole-exome sequencing analysis pipeline for integrating molecular profiles with actionable therapeutics in clinical samples. *J. Am. Med. Informatics Assoc.* ocw022 (2016). doi:10.1093/jamia/ocw022
289. Tan, O., Shrestha, R., Cunich, M. & Schofield, D. J. Application of Next-Generation Sequencing (NGS) to improve cancer management: A review of the clinical effectiveness and cost-effectiveness. *Clin. Genet.* (2017). doi:10.1111/cge.13199
290. Smith, L. D., Willig, L. K. & Kingsmore, S. F. Whole-Exome Sequencing and Whole-Genome Sequencing in Critically Ill Neonates Suspected to Have Single-Gene Disorders. *Cold Spring Harb. Perspect. Med.* **6,** a023168 (2016).
291. Lionel, A. C. *et al.* Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet. Med.* (2017). doi:10.1038/gim.2017.119
292. Swaminathan, R. *et al.* Clinical exome sequencing reports: current informatics practice and future opportunities. *J. Am. Med. Informatics Assoc.* (2017). doi:10.1093/jamia/ocx048
293. Lefebvre, M. *et al.* Genetic counselling difficulties and ethical implications of incidental findings from array-CGH: A 7-year national survey. *Clin. Genet.* (2015). doi:10.1111/cge.12696
294. Raza, S. *Defining the role of a bioinformatician*. (2014).
295. Luheshi Leila & Sobia, R. *Clinical whole genome analysis: delivering the right diagnosis*. (2014).
296. Finnegan, T. & Hall, A. *Identification and genomic data*. (2017).
297. Burton, H. *Genetic laboratory service redesign*. (2015).
298. Burton, H., Hall, A., Kroese, M. & Raza, S. *Genomics in mainstream clinical pathways*. (2017).
299. Davies, S. C. *Generation Genome: Annual Report of the Chief Medical Officer 2016*.

(2016).

300. Bourn, D. Mainstreaming genomic medicine. *Lancet (London, England)* **390,** 1486 (2017).
301. Ghazani, A. A. *et al.* Assigning clinical meaning to somatic and germ-line whole-exome sequencing data in a prospective cancer precision medicine study. *Genet. Med.* **19,** 787–795 (2017).
302. Mucchielli, A. *Dictionnaire des méthodes qualitatives en sciences humaines*. (Armand Colin, 2004).
303. Wierzbicki, J. De nouveaux moyens pour la médecine personnalisée. *Pharmaceutiques* (2014).
304. Genome Québec, Centre d'Energie Atomique & Genopole d'Evry. Communiqué de presse: Le Québec et la France concluent deux ententes de partenariat en génomique. *Press Communication* (2018). Available at: http://www.genomequebec.com/DATA/COMMUNIQUE/330_fr~v~Le_Quebec_et_la_France_concluent_deux_ententes_de_partenariat_en_genomique.pdf. (Accessed: 13th April 2018)
305. Bonafe, L. *et al.* Nosology and classification of genetic skeletal disorders: 2015 revision. *Am. J. Med. Genet. Part A* **167,** 2869–2892 (2015).
306. Yang, Y. *et al.* Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing. *Jama* **312,** 1870 (2014).
307. Yang, Y. *et al.* Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders. *N. Engl. J. Med.* **369,** 1502–1511 (2013).
308. Levy, C., Rybak, A., Cohen, R. & Jung, C. La loi Jardé, un nouvel encadrement législatif pour une simplification de la recherche clinique ? *Arch. Pédiatrie* **24,** 571–577 (2017).
309. Mamzer, M.-F. Régulation de la recherche française : mode d'emploi. *La Rev. Médecine Interne* **38,** 427–429 (2017).
310. Lyon, G. J. & Segal, J. P. Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape. *Appl. Transl. Genomics* **2,** 34–40 (2013).
311. Nicol, D. *et al.* Precision medicine: drowning in a regulatory soup? *J. Law Biosci.* **3,** 281–303 (2016).
312. Nguyen, M. T. & Charlebois, K. The clinical utility of whole-exome sequencing in the

context of rare diseases-the changing tides of medical practice. *Clin. Genet.* **88,** 313–319 (2015).

313. Samuels, M. E. *et al.* Is gene discovery research or diagnosis? *Genet. Med.* **10,** 385–390 (2008).
314. Pullman, D. & Hodgkinson, K. Genetic knowledge and moral responsibility: ambiguity at the interface of genetic research and clinical practice. *Clin. Genet.* **69,** 199–203 (2006).
315. Department of Health Education and Welfare. *The Belmont Report*. (1979).
316. Ponder, M. *et al.* Genetic research on rare familial disorders: consent and the blurred boundaries between clinical service and research. *J. Med. Ethics* **34,** 690–694 (2008).
317. Rigter, T. *et al.* Reflecting on earlier experiences with unsolicited findings: Points to consider for next-generation sequencing and informed consent in diagnostics. *Hum. Mutat.* **34,** 1322–1328 (2013).
318. Vears, D. F., Sénécal, K. & Borry, P. Reporting practices for unsolicited and secondary findings from next generation sequencing technologies: Perspectives of laboratory personnel. *Hum. Mutat.* **38,** 1–24 (2017).
319. Dheensa, S. *et al.* Management of Incidental Findings in Clinical Genomic Sequencing Studies. in *eLS* **87,** 1–7 (John Wiley & Sons, Ltd, 2016).
320. Jarvik, G. P. P. *et al.* Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between. *Am. J. Hum. Genet.* **94,** 818–826 (2014).
321. Mitchell, C. *et al.* Exploring the potential duty of care in clinical genomics under UK law. *Med. Law Int.* **17,** 096853321772196 (2017).
322. Rosenblatt, D. S. Who's on first in exome and whole genome sequencing? Is it the patient or the incidental findings? *Mol. Genet. Metab.* **110,** 1–2 (2013).
323. Burke, W., Evans, B. J. & Jarvik, G. P. Return of results: Ethical and legal distinctions between research and clinical care. *Am. J. Med. Genet. Part C Semin. Med. Genet.* **166,** 105–111 (2014).
324. Kouri, R. P. & Philips-Nootens, S. *L'intégrité de la personne et le consentement aux soins*. (Thomson Reuters Canada, 2017).
325. Philips-Nootens, S., Lesage-Jarjoura, P. & Kouri, R. P. *Elements de responsabilité civile médicale. Le droit dans le quotidien de la médecine*. (Blais, Yvon, 2007).
326. Aronson, S. J. & Rehm, H. L. Building the foundation for genomics in precision medicine.

Nature **526,** 336–342 (2015).

327. INESSS. *Exploration of Intellectual Disability and Neurodegenerative Diseases with Exome Sequencing*. (2014).
328. INESSS. *Séquençage génétique des cancers*. (2015).
329. ACMG Board of Directors. Laboratory and clinical genomic data sharing is crucial to improving genetic health care: a position statement of the American College of Medical Genetics and Genomics. *Genet. Med.* **19,** 721–722 (2017).
330. Joly, Y., Dyke, S. O. M., Knoppers, B. M. & Pastinen, T. Are Data Sharing and Privacy Protection Mutually Exclusive? *Cell* **167,** 1150–1154 (2016).
331. Stoeklé, H.-C. *et al.* Réunion de concertation pluridisciplinaire moléculaire : soin et recherche ? *Ethics, Med. Public Heal.* **2,** 343–347 (2016).
332. Rosell, A. M. C. *et al.* Not the End of the Odyssey: Parental Perceptions of Whole Exome Sequencing (WES) in Pediatric Undiagnosed Disorders. *J. Genet. Couns.* **25,** 1019–1031 (2016).
333. Robinson, J. O. *et al.* Participants and Study Decliners' Perspectives About the Risks of Participating in a Clinical Trial of Whole Genome Sequencing. *J. Empir. Res. Hum. Res. Ethics* **11,** 21–30 (2016).
334. Carver, R. B., Castéra, J., Gericke, N., Evangelista, N. A. M. & El-Hani, C. N. Young Adults' Belief in Genetic Determinism, and Knowledge and Attitudes towards Modern Genetics and Genomics: The PUGGS Questionnaire. *PLoS One* **12,** e0169808 (2017).
335. Anderson, J. A. *et al.* Parents perspectives on whole genome sequencing for their children: qualified enthusiasm? *J. Med. Ethics* **43,** medethics-2016-103564 (2016).
336. Clift, K. E. *et al.* Patients' views on incidental findings from clinical exome sequencing. *Appl. Transl. genomics* **4,** 38–43 (2015).
337. Halverson, C. M., Clift, K. E. & McCormick, J. B. Was it worth it? Patients' perspectives on the perceived value of genomic-based individualized medicine. *J. Community Genet.* **7,** 145–152 (2016).
338. Lupo, P. J. *et al.* Patients? perceived utility of whole-genome sequencing for their healthcare: findings from the MedSeq project. *Per. Med.* **13,** 13–20 (2016).
339. Jamal, L. *et al.* When bins blur: Patient perspectives on categories of results from clinical whole genome sequencing. *AJOB Empir. Bioeth.* **0,** (2017).

340. Gray, S. W. *et al.* Oncologists' and cancer patients' views on whole-exome sequencing and incidental findings: results from the CanSeq study. *Genet. Med.* **18,** 1011–1019 (2016).
341. National Human Genome Research Institute. The Cost of Sequencing a Human Genome. (2016). Available at: https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/. (Accessed: 24th January 2017)
342. Kim, J. *et al.* Good Laboratory Standards for Clinical Next-Generation Sequencing Cancer Panel Tests. *J. Pathol. Transl. Med.* **51,** 191–204 (2017).
343. Bennetts, B. *et al.* Quality standards for DNA sequence variation databases to improve clinical management under development in Australia. *Appl. Transl. Genomics* **3,** 54–57 (2014).
344. Weiss, M. M. *et al.* Best Practice Guidelines for the Use of Next-Generation Sequencing Applications in Genome Diagnostics: A National Collaborative Study of Dutch Genome Diagnostic Laboratories. *Hum. Mutat.* **34,** 1313–1321 (2013).
345. Health Council of the Netherlands. *Next generation sequencing in diagnosis*. (2015).
346. Kalia, S. S. *et al.* Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet. Med.* **19,** 249–255 (2017).
347. Li, M. M. *et al.* Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J. Mol. Diagn.* **19,** 4–23 (2017).
348. Roy, S. *et al.* Standards and Guidelines for Validating Next-Generation Sequencing Bioinformatics Pipelines. *J. Mol. Diagnostics* **20,** 4–27 (2018).
349. Meslin, E. M. & Garba, I. International Collaboration for Global Public Health. in *Public Health Ethics: Cases Spanning the Globe* (eds. H. Barrett, D. et al.) **3,** 241–284 (Springer International Publishing, 2016).
350. Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé. *Avis 124: Réflexion éthique sur l'évolution des tests génétiques liée au séquençage de l'ADN humain à très haut débit*. (2016).
351. Viens, E.-J. Le consentement des personnes vulnérables à la recherche : regard sur les

amendements et les omissions de l'article 21 du code civil du Québec. (Université de Sherbrooke, 2015).

352. Jaillon, P. & Demarez, J.-P. L'histoire de la genèse de la loi Huriet-Sérusclat de décembre 1988. *médecine/sciences* **24,** 323–327 (2008).
353. Carlson, R. V, Boyd, K. M. & Webb, D. J. The revision of the Declaration of Helsinki: past, present and future. *Br. J. Clin. Pharmacol.* **57,** 695–713 (2004).
354. Pigeon, A. Les enjeux juridiques de l'accès à l'information génétique. (L'Université Toulouse 1 Capitole, 2016).
355. International Bioethics Committee. Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights. *United Nations Educ. Sci. Cult. Organ.* 1–30 (2015).
356. Mamzer Bruneel, M.-F. & Hervé, C. La requalification des données de soins en données de recherche : enjeux éthiques et blocages normatifs. *Ethics, Med. Public Heal.* **3,** 83–89 (2017).
357. Agence de la Biomédecine. *Rapport sur l'application de la loi de bioéthique*. (2018).
358. Salman, S. De certains enjeux en responsabilité médicale des oncologues. *Rev. droit l'Université Sherbrooke* **45,** 367–416 (2015).
359. Zawati, M. Liability and the Legal Duty to Inform in Research. in *Routledge Handbook of Medical Law and Ethics* (eds. Joly, Y. & Knoppers, B. M.) (Routledge, 2014).
360. DestinationSante. Cancer : comprendre le droit à l'oubli. *La Depeche* (2016).
361. Le Monde Santé. Le « droit à l'oubli » pour les anciens malades du cancer voté. *Le Monde* (2015).
362. Centres de Référence et Filières de Santé Maladies Rares. *Rapport d'Activité 2017 - Maladies Rares*. (2017).
363. Institut National du Cancer. *Plan Cancer 2014-2018: 4ème Rapport au Président de la République*. (2018).
364. Krahn, M., Cerino, M., Campana-Salort, E. & Cossée, M. Vers une homogénéisation nationale des analyses par NGS dans la démarche diagnostique pour les myopathies. *médecine/sciences* **33,** 30–33 (2017).
365. Claeys, A. & Vialiatte, J.-S. *Les progrès de la génétique : vers une médecine de précision ? Les enjeux scientifiques, technologiques, sociaux et éthiques de la médecine personnalisée*. (2014).

366. Human Genetics Commission. *Increasing options, informing choice: A report on preconception genetic testing and screening*. (2011).
367. Galibert, F. & Jarry, B. *Rapport et recommandations sur la mise en œuvre en France des techniques de séquençage de nouvelle génération*. (2016).
368. Philippe, E. Discours du Premier Ministre, Plan France Médecine Génomique 2025. (2017).
369. Simon-Bouy, B. & Caron, O. L'accès à la médecine génomique pour tous les patients : rêve ou réalité ? *Gynécologie Obs. Fertil. Sénologie* **45,** 187–189 (2017).
370. Robert-Géraudel, A. Santé : mais où sont passés les crédits maladies rares ? *Faire Face* (2018).
371. Institute of Health Economics. *Personalized Medicine - Policy Gaps and system Readyness: Summary report of a roundtable discussion*. (2012).
372. CADTH. *Next Generation DNA Sequencing: A Review of the Cost Effectiveness and Guidelines*. (2014).
373. RSSPQ. *Parcours d'intégration des tests diagnostiques en soins de santé personnalisés au Québec. Accueillir la médecine de demain*. (2015).
374. Bourassa Forcier, M. & Abbamonte, C. *Le Québec chef de file dans le développement et l'intégration des soins de santé personnalisés : la règlementation et les politiques québécoises actuelles le permettent-elles ?* (2015).
375. INESSS. *MYRIAD MYRISKMD – Panel de 25 gènes associés aux cancers héréditaires analysés par séquençage de nouvelle génération*. (2016).
376. INESSS. *Panel de huit gènes - analyse de mutations somatiques par séquençage de nouvelle génération pour le traitement personnalisé du cancer*. (2016).
377. Sido, B. & Le Déaut, J.-Y. *Rapport au nom de l'OPECST sur LES PROGRÈS DE LA GÉNÉTIQUE : VERS UNE MÉDECINE DE PRÉCISION ? LES ENJEUX SCIENTIFIQUES, TECHNOLOGIQUES, SOCIAUX ET ÉTHIQUES DE LA MÉDECINE PERSONNALISÉE*. (2014).
378. Commission de l'éthique en science et en technologie. *Les soins de santé 'personnalisés': prudence et balises*. (2014).
379. Strauss, K. A. *et al.* Genomic diagnostics within a medically underserved population: efficacy and implications. (2017). doi:10.1038/gim.2017.76

380. Hayeems, R. Z. *et al.* Care and cost consequences of pediatric whole genome sequencing compared to chromosome microarray. *Eur. J. Hum. Genet.* **25,** 1303–1312 (2017).
381. Stavropoulos, D. J. *et al.* Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine. *npj Genomic Med.* **1,** 15012 (2016).
382. Mattick, J. S., Dinger, M., Schonrock, N. & Cowley, M. Whole genome sequencing provides better diagnostic yield and future value than whole exome sequencing. *Med. J. Aust.* 1 (2018). doi:10.5694/mja17.01176
383. Meienberg, J., Bruggmann, R., Oexle, K. & Matyas, G. Clinical sequencing: is WGS the better WES? *Hum. Genet.* **135,** 359–362 (2016).
384. Hegde, M. *et al.* Development and Validation of Clinical Whole-Exome and Whole-Genome Sequencing for Detection of Germline Variants in Inherited Disease. *Arch. Pathol. Lab. Med.* **141,** 798–805 (2017).
385. LaDuca, H. *et al.* Exome sequencing covers >98% of mutations identified on targeted next generation sequencing panels. *PLoS One* **12,** e0170843 (2017).
386. Shamseldin, H. E. *et al.* Increasing the sensitivity of clinical exome sequencing through improved filtration strategy. *Genet. Med.* (2016). doi:10.1038/gim.2016.155
387. Du, C. *et al.* Explorations to improve the completeness of exome sequencing. *BMC Med. Genomics* **9,** 56 (2016).
388. Lelieveld, S. H., Veltman, J. A. & Gilissen, C. Novel bioinformatic developments for exome sequencing. *Hum. Genet.* **135,** 603–614 (2016).
389. Greg Breining. Rare Diseases Difficult to Diagnose, Cures Hard to Come By. *AAMC News* (2017).
390. Cook-Deegan, R., Ankeny, R. A., Jones, K. M. & Maxson Jones, K. Sharing Data to Build a Medical Information Commons: From Bermuda to the Global Alliance. *Annu. Rev. Genomics Hum. Genet.* **18,** annurev-genom-083115-022515 (2017).
391. Phillips, K. A. *et al.* Making genomic medicine evidence-based and patient-centered: a structured review and landscape analysis of comparative effectiveness research. *Genet. Med.* **19,** 1081–1091 (2017).
392. Curnutte, M. A. *et al.* Developing context-specific next-generation sequencing policy. *Nat. Biotechnol.* **34,** 466–470 (2016).
393. Deverka, P. A. & Dreyfus, J. C. Clinical integration of next generation sequencing:

Coverage and reimbursement challenges. *J. Law, Med. Ethics* **42,** 22–41 (2014).

394. Angrist, M. & Jamal, L. Living laboratory: whole-genome sequencing as a learning healthcare enterprise. *Clin. Genet.* **87,** 311–8 (2015).
395. Delaney, S. K. *et al.* Toward clinical genomics in everyday medicine: perspectives and recommendations. *Expert Rev. Mol. Diagn.* **16,** 521–532 (2016).
396. Chambers, D. A., Feero, W. G. & Khoury, M. J. Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System. *JAMA* **315,** 1941 (2016).
397. Cook-Deegan, R. & McGuire, A. L. Moving beyond Bermuda: sharing data to build a medical information commons. *Genome Res.* **27,** 897–901 (2017).
398. Phillips, K. A. Evolving Payer Coverage Policies on Genomic Sequencing Tests. *JAMA* (2018). doi:10.1001/jama.2018.4863
399. Jensen, T. S. *et al.* Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N). 1–128 (2017).
400. Ashford, M. Labs Confront Legal Risks Posed by Genetic Variant Classification, Reporting. *GenomeWeb* (2017).
401. Ray, T. In Quest/Athena Wrongful Death Suit, District Court Judge Holds Hearing on Motion to Dismiss. *GenomeWeb* (2017).
402. Conley, J. M. & Coons, L. Williams v . Athena Motion to Dismiss Hearing — SC Supreme Court May Be Asked to Decide Whether a Diagnostic Laboratory Qualifies as a Healthcare. *Genomics Law Report* (2017).
403. Ray, T. Mother's Negligence Suit Against Quest's Athena Could Broadly Impact Genetic Testing Labs. *GenomeWeb* (2016).
404. Commo, F. *et al.* Impact of centralization on aCGH-based genomic profiles for precision medicine in oncology. *Ann. Oncol.* **26,** 582–588 (2015).
405. Friedman, J. M. *et al.* Genomic newborn screening: public health policy considerations and recommendations. *BMC Med. Genomics* **10,** 9 (2017).
406. Ulm, E., Feero, W. G., Dineen, R., Charrow, J. & Wicklund, C. Genetics Professionals' Opinions of Whole-Genome Sequencing in the Newborn Period. *J. Genet. Couns.* **24,** 452–463 (2015).
407. Howard, H. C. *et al.* Whole-genome sequencing in newborn screening? A statement on the continued importance of targeted approaches in newborn screening programmes. *Eur.*

J. Hum. Genet. **23,** 1593–1600 (2015).

408. Coutor, O. & Vulliet-Tavernier, S. *Les données génétiques*. (La Documentation Française, 2017).
409. Bombard, Y., Abelson, J., Simeonov, D. & Gauvin, F.-P. Citizens' perspectives on personalized medicine: a qualitative public deliberation study. *Eur. J. Hum. Genet.* **21,** 1197–1201 (2013).
410. Wilson, B. & Nicholls, S. G. The Human Genome Project, and recent advances in personalized genomics. *Risk Manag. Healthc. Policy* **8,** 9 (2015).
411. Johnston, H. R. *et al.* Identifying tagging SNPs for African specific genetic variation from the African Diaspora Genome. *Sci. Rep.* **7,** 46398 (2017).
412. Belbin, G. M. *et al.* Genetic identification of a common collagen disease in Puerto Ricans via identity-by-descent mapping in a health system. *Elife* **6,** e25060 (2017).
413. Martin, A. R. *et al.* Human Demographic History Impacts Genetic Risk Prediction across Diverse Populations. *Am. J. Hum. Genet.* **100,** 635–649 (2017).
414. FDA. *Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests—Preliminary Discussion Paper*. **3,** (2015).
415. FDA. *Use of Standards in FDA Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases, Draft Guidance for Stakeholders and Food and Drug Administration Staff*. (2016).
416. Sharfstein, J. FDA Regulation of Laboratory-Developed Diagnostic Tests. *JAMA* **313,** 667 (2015).
417. Lin, D. Fda-Approved Next-Generation Sequencing System Could Expand. *Am. J. Med. Genet. Part A* **164,** 95424946 (2014).
418. Ratner, M. FDA pushes for control over laboratory-developed tests. *Nat. Biotechnol.* **32,** 855–855 (2014).
419. Litwack, E. D., Mansfield, E. & Shuren, J. The FDA and Genetic Testing. *N. Engl. J. Med.* **372,** 2273–2274 (2015).
420. Evans, B. J., Burke, W. & Jarvik, G. P. The FDA and Genomic Tests — Getting Regulation Right. *N. Engl. J. Med.* **372,** 2258–2264 (2015).
421. FDA. *Discussion Paper on Laboratory Developed Tests (LDTs)*. (2017).

APPENDICES

Appendix A: Other publications

The contribution of the thesis author to other published manuscripts during the thesis period is listed below.

1. **Bertier G**, Zawati MH, Joly Y. The Role of Whole Genome and Whole Exome Sequencing in Preventive Genomic Sequencing Programs. Am J Bioeth [Internet]. 2015 Jan [cited 2015 Nov 4];15(7):22–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26147258

2. Sénécal K, Vears DF, **Bertier G**, Knoppers BM, Borry P. Genome-based newborn screening: a conceptual analysis of the best interests of the child standard. Per Med [Internet]. 2015 Sep 3 [cited 2015 Oct 6];12(5):439–41. Available from: http://www.futuremedicine.com/doi/abs/10.2217/PME.15.28

3. Dheensa S, Shkedi-Rafid S, Crawford G, **Bertier G**, Schonstein L, Lucassen A. Management of Incidental Findings in Clinical Genomic Sequencing Studies. In: eLS [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2016. p. 1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26439717

4. Julia S, **Bertier G**, Cambon-Thomsen A. Quand l'anticipation devient plurielle : la complexité des données génomiques à l'épreuve des pratiques professionnelles. Rev française d'éthique appliquée [Internet]. 2016 [cited 2016 Jun 24];N° 2(2):19–28. Available from: https://www.cairn.info/revue-francaise-d-ethique-appliquee-2016-2-page-19.htm

5. **Bertier G**, Carrot-Zhang J, Ragoussis V, Joly Y. Integrating precision cancer medicine into healthcare—policy, practice, and research challenges. Genome Med [Internet]. 2016

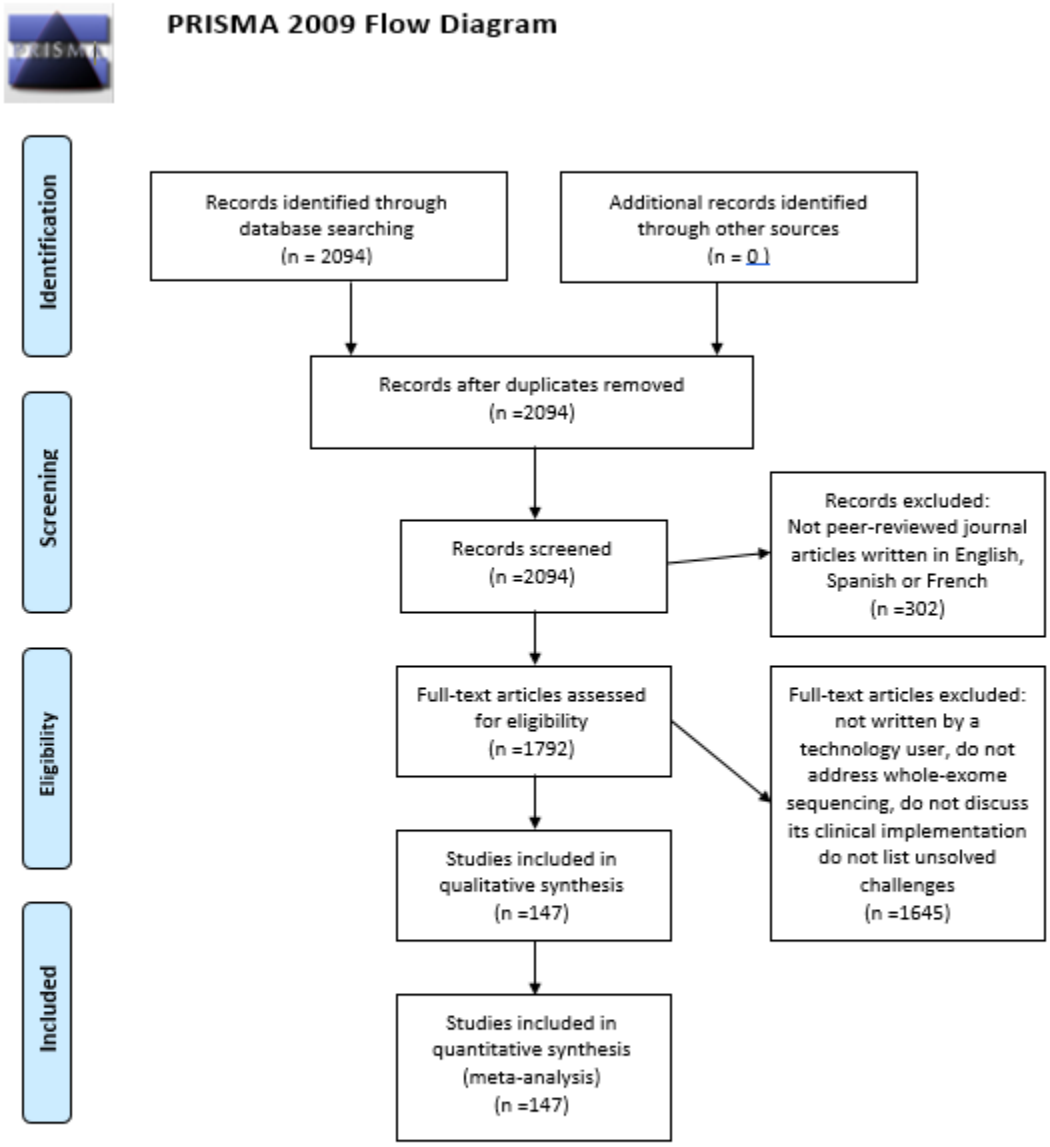
Dec 24 [cited 2016 Oct 25];8(1):108. Available from: http://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0362-4

6. Murdoch B, Ravitsky V, Ogbogu U, Ali-Khan S, **Bertier G**, Birko S, Bubela T, De Beer J, Dupras C, Ellis M, Granados Moreno P, Joly Y, Kamenova K, Master Z, Marcon A, Paulden M, Rousseau F, Caulfield T. Non-invasive Prenatal Testing and the Unveiling of an Impaired Translation Process. J Obstet Gynaecol Canada [Internet]. 2017 Jan;39(1):10–7. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1701216316395937

Appendix B: Supplementary material for Chapter 2

Additional file 1: PRISMA flow diagram

Unsolved challenges of clinical whole-exome sequencing: A systematic literature review of end-users' views. Bertier *et al.*



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Additional file 2: PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not Applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Not Applicable
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Not Applicable
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not Applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not Applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not Applicable

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not Applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not Applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5-6, tables 1 and 2, flow diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not Applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not Applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not Applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not Applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not Applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Article submission information

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Additional file 3: Full articles dataset

The dataset is available at
https://static-content.springer.com/esm/art%3A10.1186%2Fs12920-016-0213-6/MediaObjects/12920_2016_213_MOESM3_ESM.xlsx

Appendix C: Supplementary material for Chapter 4

Additional file 1: Details on data collection and analysis methodology

This additional file submitted with the manuscript entitled: Clinical exome sequencing in France and Quebec: what are the challenges? What does the future hold?

Information sources

Data collection started in November 2015 and was completed in July 2017. The case studies are based on three main sources of information: interviews, project presentations and project documentation.

In each case, GB conducted interviews with at least three stakeholders, namely: the PIs leading the project, a bioinformatician who analyses patients' WES data, and a clinical geneticist or a clinician, who produces the WES report and communicates results to patients or their referring clinician. We designed partly overlapping interview guides (see interview guide below) for each type of stakeholder for one hour long semi-structured interviews. A total of 23 interviews were completed and transcribed verbatim by a professional transcriber. 22 interviews were conducted in French and 1 in English.

GB attended a total of 10 project meetings in which project strategies or project results were discussed.

Finally, we collected a variety of documents which provide a detailed overview of the projects' design, data management plan and results. These include: grant proposals submitted, PowerPoint presentations, consent forms, CES analysis reports used to inform doctors and patients of the test results, and bioinformatics analysis pipelines.

Analysis strategy

The information collected in each case was coded in NVivo. First, a novel thematic tree was generated directly from the data, using an inductive method[a]. Second, this thematic tree was compared to one generated from previous publications[b],[c], following the deductive analysis method[d]. We also explored similarities and differences across French and Quebec cases, across case types, and across interviewed stakeholders. Inter-rater validity was obtained in two ways: first, the thematic tree obtained through the deductive analysis was discussed with two independent researchers who are experienced with qualitative data analysis and with NVivo, but were not involved in either the project design or the data collection. Second, the latter researcher co-coded one interview. All differing codes were discussed with the lead author (GB) and the thematic tree was adapted based on consensus coding.

Interview Guide

Questions	**PI**	**Clinician**	**Bioinformatician**
Introduction	What is your current position, and how long have you occupied it?		
	Is WES used in your institution for research or for clinical purposes		
The project	Describe where the idea of the project comes from	Since when/why/how are you involved in the project?	
	Describe the project rationale	Please provide a description of the project from your perspective	
	How is the project funded?		
	How is the project advancement monitored?		
Data production, analysis, reporting	Could you describe briefly how WES data is produced-analysed-reported	Walk me through a typical patient referral process	Walk me through a typical data analysis process
	Who is in charge of data analysis?	Describe briefly if/how you discuss results with the project team, and how you	Who finally decides which results are reported?

[a] Mucchielli A : Dictionnaire des méthodes qualitatives en sciences humaines. Ed 2 Paris, Armand Colin, 2004.
[b] Bertier G, Hétu M, Joly Y: Unsolved challenges of clinical whole-exome sequencing: a systematic literature review of end-users' views. BMC Med Genomics 2016;9:52.
[c] Bertier G, Sénécal K, Borry P, Vears DF: Unsolved challenges in pediatric whole-exome sequencing: A literature analysis. Crit Rev Clin Lab Sci 2017;54:134–142.
[d] Elo S, Kyngäs H: The qualitative content analysis process. J Adv Nurs 2008;62:107–15.

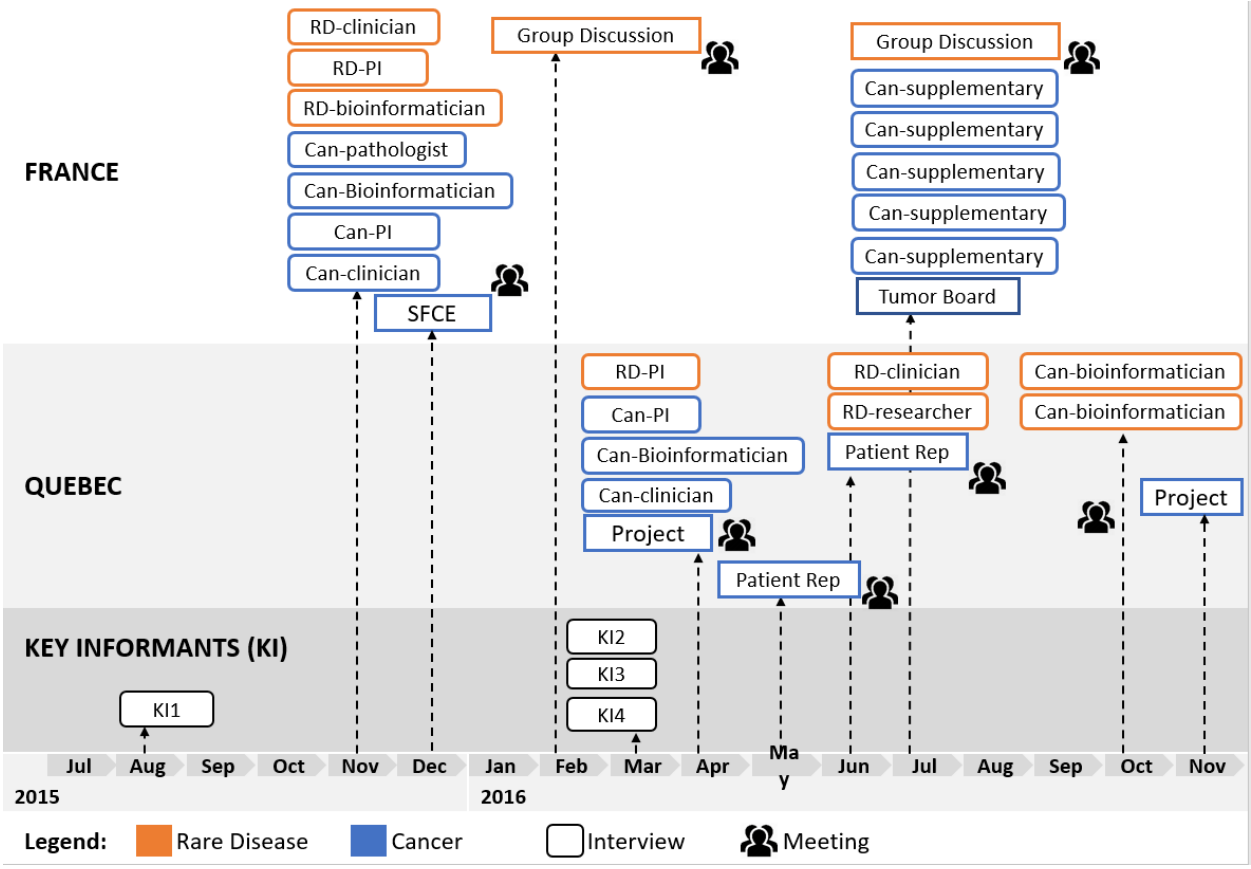
		communicate results to the patients and their families	
	Are you personally involved in data interpretation?		Who do you report the results to?
	What is a typical timeline between reception of the raw data and reporting?		
	Are WES data reused in research or reanalysed for further patient care?		
Guidelines	What forms, protocols, guidelines (internal or external) did you have to follow to set up the use of WES data in the project	What forms, protocols, guidelines (internal or external) do you follow to include patients in the project and to report the data to patients and their families?	What forms, protocols, guidelines (internal or external) did you have to follow to set up the use of WES data in the project
	What is your opinion on these guidelines?		
The present	What is the current progress of the project?		
	What is main challenge of the project, and why?		
	What would be the main indicator of the success of the project? How/when do you think this will happen?		
	Should WES be introduced in routine clinical care for cancer/rare disease patients in France/Quebec?		
The future	What do you expect will change in the next five years?		

Additional file 2: Data collection timeline

This figure was not submitted with the manuscript entitled: Clinical exome sequencing in France and Quebec: what are the challenges? What does the future hold?

6) Figure S.1: Data collection timeline

Figure



RD: Rare Diseases

Can: Cancer

SFCE: Société Française de lutte contre les Cancers et les leucémies de l'Enfant et l'adolescent

Patient Rep : Reporting of WES results to medical doctor (Patient report)

PI: Principal Investigator

KI: Key Informants

Additional file 3: Supplementary results

These additional results were not submitted with the manuscript entitled: Clinical exome sequencing in France and Quebec: what are the challenges? What does the future hold?

We are pioneers

Throughout data collection, stakeholders described the way their team was performing clinical WES with a sense of pride and excitement, as well as occasional discomfort or consciousness that this organization or action was non-standard or controversial. The 'pioneer' theme, which was a recurrent one in all four teams, was associated with a sense that France and Quebec are latecomers or move more slowly than other countries or provinces in clinical genomics, and that teams are therefore pioneers in the national context because they are the only ones performing the test. Therefore, they must establish new standards and methods, and that they contribute to making things change in the right direction at the national level.

➢ We are different

In both RD teams, members explained that they were the only ones using WES as a clinical diagnosis test, in FR or in QC, and even Canada as a whole. Indeed, no other teamsoffer this test specifically in patient care, but rather offer Array CGH tests, focused genetic tests or large gene panels. In Cancer teams, rather than the technology itself, it was the process of collecting tumor cells, extracting DNA and performing the analysis within a short time-frame which was described as unique. In QC, it was mostly the short turnaround time and the high patients' participation rate that was described as the defining characteristic of the team's activity. In France, the fact that patients had to undergo a dedicated biopsy for the project was described as the most unique feature.

"[…] but really, the clinical analysis of the exome, in diagnosis, for now, is not deployed anywhere other than here. Which means that there is really a delay in terms of organisation and deployment because of a lack of training. A lack of means too, of course, but also because of a lack of training of biologists, who are not trained on the exome, and also because they don't

necessarily have bioinformaticians, and so there is a very important delay. *French Rare Disease PI*

"So, there is really – we really feel a lag in terms of society and concept which is really significant compared to the US, because we are very late, and, so, professionals from the field, they are, I think, like they were in the US five or six years ago. I mean they are still in disease diagnostic, they haven't realized yet that genomics is going to be more than that. And truly, I went to Baltimore to the American congress in October, and by crossing the Atlantic I felt like I was crossing time! I had a huge cultural chock – huge, when I came back here, I said us, I won't say we're in the Middle Ages, but we are asking ourselves questions that them, they have partly, not overcome, but at least they've thought about them and moved forward." *French Rare Disease PI*

Teams in QC compared their province to Ontario because its population, and therefore the total patient demand for CES, is comparable. In addition, the two provinces also have several health institutions that could offer the test, and would benefit from organising themselves into a consortium to distribute the workload effectively throughout the province. One interviewee also described how slow to develop the clinical practice has been in Cancer compared to what is possible in research:

"[…] Because it's lagging so far behind, it seems that there's such a gap between what we do in the clinic, what is validated, I don't know how to say this, what is not… authorized…
GB: standardized?
Quebec Cancer Clinician. Yes… it's so far compared to what we do in research…"

- Home-made

Another important theme we identified was that of an implementation that is « home-made ». Bioinformatics pipelines in all four teams have been developed for the specific purposes of those projects, using a unique mix of standard and home-made software and validation parameters. The processes through which these pipelines were developed and are updated were described as « kitchen recipes », « improved by self-directed learning » *French Cancer Biochemist,* « artisanal » *French Cancer bioinformatician,* "manual" or having "started from scratch" *Quebec Cancer bioinformatician*. They were usually established progressively, a

process that took from several months to a few years, then tested and improved over time. Similarly, clinicians described the way they established their own process, timeline and filing system to regularly monitor the literature in order to interpret the clinical relevance of variants. The data interpretation process always includes discussion in a group, including clinicians, bioinformaticians, and biologists, and the results are never pulled automatically from the data. Teams also established a unique consent form and clinical report document based on available expertise, discussions within the team and institution, examples from collaborators and publications, and their interpretation of the most relevant available and applicable guidelines.

"And all this process, if you want, in terms of recruitment, filters, etc. all that was… and in terms of analysis the way in which the variants file is presented, etc.… all that is the fruit of a collaborative work within, a committee to which Dr. X, Dr Y and myself, and other collaborators has worked, so it's the fruit of four years of iteration basically." *Quebec Rare Disease Clinician*

Because the consent form and clinical reports are so unique and represent the result of significant research and discussion efforts, it was sometimes difficult for us to have access to these documents. Teams also decided how to report IFs in a similar manner, using existing guidelines, their interpretation of existing laws, and the team members' vision of what is in patients' best interest. When discussing the absence of formal local or national guidelines, Standard Operating Procedures or laws, interviewees also described the efforts they made to choose the right guideline to apply in their context.

"There are professional societies at many levels, you should… you should have a solid rationale in the choices you make, but then… the most important thing is not build things on your own without external support. In short, we don't do anything that hasn't already been proven, and that is not supported by a leading group in the field. As I told you, the Broad for bioinformatics, Baylor for proband only exome diagnosis, in it's analysis and interpretation strategy EuroGenTest[a] for quality control, samples management and the design of reports for clinicians, and the ACMG[b] for secondary findings categorization. So we took that we were interested in from a little bit everywhere, to try to be as standard and as representative of a

[a] http://www.eurogentest.org/index.php?id=160
[b] American College of Medical Genetics and Genomics

functioning model as possible, because that's what is needed[…]the idea is that we can move on, based on things that are strong, robust, demonstrated, by people who are professionals, while we wait for our scholarly society to either confirm it, partially or entirely, and in this case we will follow what is promulgated… adhering with what is promulgated by a supervisory scholarly society. For now, its not the case." *French Rare Disease Clinician*

- Impact on change in policy

Team members described several actions they were taking in their country/province to solve the issues described in 4.5.2 Main challenges in "leveling up". The first direct way in which they are contributing is by setting up clinical WES in their institution, collecting evidence to demonstrate that it works, and then by offering the test as a service to other institutions. Since the beginning of this study, all teams have published several research articles based on the results they obtained by analysing their patients' WES data. Their scientific contributions range from improving the understanding of specific diseases to describing their bioinformatic analysis and interpretation pipeline. Additional actions included:

- Talking to staff at the MoH, discussing potential benefits of CES and genomic sequencing technologies in general. *French Rare Disease PI* and *Quebec Rare Disease PI.*
- Developing and offering training to practitioners, either in the form of a module tailored to clinicians (described as a "mass-communication campaign" to ensure clinicians are "less afraid" and have more reasonable expectations towards NGS technologies *French Cancer Bioinformatician*) or by designing a new training program in bioinformatics (Coordination of the University Diploma entitled «High-throughput sequencing and genetic diseases» *French Rare Disease Bioinformatician*).
- Developing new data analysis software tools and sharing them with the community (such as a variant-calling algorithm, *French Cancer Bioinformatician*)
- Engaging in collaborations with national societies and pharmaceutical companies to improve the way cancer clinical trials are designed, and give input on which pathways are important targets. (*French Cancer PI*)
- Participation in a public-private partnership to establish an integrated tool for high-throughput sequencing interpretation, ranging from quality control to variant selection and interpretation through data mining. (*French Cancer Bioinformatician*)

- Designing new implementation/proof of concept research projects on specific aspects of CES, such as ethical issues, ideal consent procedures, or medico-economical aspects of CES compared to other tests.

Discussion: Children and adults

The vast majority of patients who go through CES in the four teams studied here are pediatric patients. Although the literature on ethical, legal and social issues of pediatric research and clinical care abounds, the stakeholders we interviewed did not highlight many specific issues in dealing with this vulnerable population. This is probably partly explained by the fact that all interviewees were accustomed to working with children. However, cancer being considered a RD in children, there was quite a lot of discussion within the cancer teams on the dreadful lack of data and clinical research on pediatric cancers compared to adult cancers, especially as research has shown that the disease has very different biological hallmarks and impacts on the two populations[a,b.] One stakeholder from the Quebec Rare Disease team also explained that IFs have to be managed differently in children and adults, because whereas adults are free to refuse to be informed of any finding, highly impactful mutations that are actionable in childhood have to be reported to parents, according to the CCMG guideline[c]. According to the same guideline, if sequencing is done in trios (analysing the proband as well as both their parents), adult patients can choose to receive either only variants linked to their child's condition, those plus any medically actionable mutations for themselves, or all variants (including predisposition for untreatable neurodegenerative diseases).

---

[a] Jones, C. et al. Pediatric high-grade glioma: biologically and clinically in need of new thinking. Neuro. Oncol. 19, now101 (2016).
[b] Castel, D., Grill, J. & Debily, M.-A. Histone H3 genotyping refines clinico-radiological diagnostic and prognostic criteria in DIPG. *Acta Neuropathol.* **131,** 795–796 (2016).
[c] Boycott, K. *et al.* The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. *J. Med. Genet.* **52,** 431–437 (2015)

Additional file 4: Ethics approvals

CEEI - IRB

Comité d'Evaluation Ethique de l'Inserm

IRB00003888

Instituts thématiques — Inserm — Institut national de la santé et de la recherche médicale

Nos réf: CD / KM 15 - 99
Dossier suivi par :
Christine DOSQUET -CEEI
@ : ceei@inserm.fr

Mme Gabrielle Bertier
Inserm UMR1027
Université Toulouse III Paul Sabatier
37 Allées Jules Guesde
31000 Toulouse

Paris, le 16 octobre 2015

Chère Madame,

Veuillez trouver ci-joint votre **avis n°15-253** pour votre projet intitulé :

"Implémentation clinique du séquençage de l'exome complet : analyse multidisciplinaire de la trajectoire des données",

examiné lors de la réunion du CEEI du 6 octobre 2015.

Veuillez agréer, Chère Madame, l'expression de mes salutations distinguées.

Katy MAIN
Secrétaire du CEEI

CEEI - IRB

Comité d'Evaluation Ethique de l'Inserm

IRB00003888

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Nos réf: CD/KM 15 - 99
Dossier suivi par :
Christine DOSQUET -CEEI
@ : ceei@inserm.fr

Mme Gabrielle Bertier
Inserm UMR1027
Université Toulouse III Paul Sabatier
37 Allées Jules Guesde
31000 Toulouse

Paris, le 6 octobre 2015

Pour faire valoir à qui de droit
Avis N°15-253

Madame,

Le Comité d'Evaluation Ethique de l'Inserm, Institutional Review Board (IRB00003888) de l'Inserm (IORG0003254, FWA00005831) a donné un avis favorable pour votre projet intitulé :

"Implémentation clinique du séquençage de l'exome complet : analyse multidisciplinaire de la trajectoire des données",

Le CEEI rappelle que l'investigateur s'engage à respecter le protocole déposé et à suivre ses recommandations.

Avec mes salutations distinguées,

Christine DOSQUET
Présidente du CEEI/IRB

CEEI - IRB

Comité d'Evaluation Ethique de l'Inserm

IRB00003888

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

Nos réf: CD / KM 15 - 99
Dossier suivi par :
Christine DOSQUET -CEEI
@ : ceei@inserm.fr

Mme Gabrielle Bertier
Inserm UMR1027
Université Toulouse III Paul Sabatier
37 Allées Jules Guesde
31000 Toulouse

Paris, October 6th 2015

To whom it may concern
Opinion number 15-253

Dear Madam,

The ethics evaluation committee of Inserm (IORG0003254, FWA00005831), the Institutional Review Board (IRB00003888) of the French Institute of medical research and Health, has reviewed and approved the research project entitled:

"Clinical implementation of whole-exome sequencing : a multidisciplinary analysis of the data trajectory"

The investigator undertakes to respect the protocol and to follow the recommendations proposed by the ethics evaluation committee.

Yours sincerely,

Christine DOSQUET
IRB President

McGill

Faculty of Medicine
3655 Promenade Sir William Osler #633
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler #633
Montréal, QC H3G 1Y6

Fax/Télécopieur: (514) 398-3870
Tél/Tel: (514) 398-3124

December 4, 2015

Dr. Yann Joly
Human Genetics
740 Dr. Penfield
Montreal, Quebec H3A 0G1

RE: IRB Review Number A12-M66-15A
Clinical implementation of whole-exome sequencing: a multidisciplinary analysis of the data trajectory

Dear Dr. Joly,

Thank you for submitting the above study for IRB review.

As this study involves no more than minimal risk, and in accordance with Articles 2.9 and 6.12 of the 2nd Edition of the Canadian Tri-Council Policy Statement of Ethical Conduct for Research Involving Humans (TCPS 2) and U.S. Title 45 CFR 46, Section 110 (b), paragraph (1), we are pleased to inform you that ethics approval for the study protocol (November 2015) is provided via an expedited review by the IRB Chair on December 4, 2015. The ethics approval is valid until **December 2016**. The study proposal will be presented for corroborative approval at the next meeting of the Committee and a certification document will be issued to you at that time.

A review of all research involving human subjects is required on an annual basis in accord with the date of initial approval. The annual review should be submitted at least one month before **December 2016**. Please inform the IRB promply of any modifications that may occur to the study over the next twelve months.

Sincerely,

Roberta Palmour

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: A12-M66-15A