Evaluating the gap between research ethics review and data sharing in the pediatric infrastructure sciences: a case of big data and little ethics?

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March 2019

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A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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Abstract

BACKGROUND: Clinical progress in genomics-enabled learning health systems relies on the production, use and exchange of data, including from children. The policies and practices guiding proportionate governance of such production, access and exchange are, however, markedly limited in the pediatric genomics space. The need for policy-practice coherence in genomic data sharing can be accentuated when involving children, from whom data may require special protections. Absent understanding the ethical-legal bases upon which responsible pediatric data sharing rests, present and future children may not reap the benefits of a healthcare system that continuously 'learns' from the production, use and exchange of their data. The purpose of this thesis is twofold: to identify the ethical, legal, social and scientific factors that enable 'responsible' genomic and associated clinical data sharing involving children; and to develop a policy framework guiding responsible sharing for the pediatric genomics community in Canada. **METHODS**: A systematic review of reasons was combined with policy Delphi methods to develop the *K*ey *I*mplications of *D*ata *S*haring (KIDS) framework for pediatric genomics. Thematic content, and descriptive statistical analyses were used to understand how 12 Canadian pediatricians, genomic researchers, ethicists and bioethics scholars prioritize the ethical-legal, social and scientific policy positions outlined in the KIDS framework. **RESULTS**: The panel reached consensus on 9 of 12 original policy positions identified in the systematic review and refined during a key informant committee meeting of international data sharing experts. Discrepant views related to informational risks, data access and oversight of anonymized versus coded genomic data were primary sources of dissention. **CONCLUSION**: This thesis makes two contributions to the theory and practice of responsible data sharing involving children in Canada. First, it suggests that skepticism of data anonymization drives support for more stringent access controls and oversight when data involve children. Second, greater emphasis on data accountability—coupled with data security—could serve as a more effective policy lever to preserve patient trust in data sharing given rapid progress in computation, ensuring children remain at the forefront of genomic innovation.

Résumé

CONTEXTE: Les progrès cliniques dans les systèmes de santé apprenants favorisés par la génomique reposent sur la production, l'utilisation et l'échange de données, y compris celles provenant d'enfants. Les politiques et pratiques guidant la « gouvernance proportionnée » de cette production, de cet accès et de ces échanges font toutefois nettement défaut dans l'espace de la génomique pédiatrique. La nécessité d'une cohérence entre les politiques et les pratiques en matière de partage de données génomiques peut être accentuée lorsque des enfants sont impliqués, ceux-ci pouvant nécessiter des protections spéciales. En l'absence d'une compréhension des bases éthiques et légales sur lesquelles repose un partage responsable des données pédiatriques, les enfants actuels et futurs ne peuvent pas profiter des avantages d'un système de santé qui « apprend » continuellement de la production, de l'utilisation et de l'échange de leurs données. L'objet de cette thèse est donc double: identifier les facteurs éthiques, juridiques, sociaux et scientifiques permettant un partage « responsable » de données génomiques et cliniques associées impliquant des enfants; et élaborer un cadre guidant le partage responsable des données pour la communauté de la génomique pédiatrique au Canada. **MÉTHODES**: Une revue systématique des arguments a été combinée avec la méthode « Delphi de politiques publiques » (*Policy Delphi*) pour développer le cadre de KIDS (Key Implications of Data Sharing) pour la génomique pédiatrique. L'analyse thématique de contenu et des analyses statistiques descriptives ont été utilisées pour comprendre comment 12 pédiatres, chercheurs en génomique, éthiciens et chercheurs en bioéthique du Canada accordent la priorité à différentes positions politiques définies, dans le cadre KIDS, en termes éthiques, juridiques, sociaux et scientifiques. **RÉSULTATS**: Le panel a atteint un consensus sur 9 des 12 positions de politiques. Les points de vue divergents liés aux risques informationnels, à l'accès aux données et à la surveillance des données génomiques anonymisées par rapport aux données codées ont été les principales sources de dissension. **CONCLUSION**: Cette thèse apporte deux contributions à la théorie et à la pratique du partage responsable de données impliquant des enfants au Canada. La première suggère que le scepticisme concernant l'anonymisation des données entraine l'appui à des mesures de contrôles d'accès et de surveillance plus strictes lorsque les données impliquent des enfants. Deuxièmement, une plus grande importance accordée à la responsabilisation à l'égard des données – associée à la sécurité des données – pourrait constituer un levier politique plus efficace pour préserver la confiance des patients dans le partage des données face aux progrès rapides des

capacités de calcul, garantissant ainsi que les enfants restent au premier plan de l'innovation génomique.

Acknowledgements

Eight allegorical statues, all women, stand on guard in the Main Reading Room of the Library of Congress in Washington D.C. as if to remind researchers of the magnitude of their responsibility for translating knowledge the books within the library contain. One of these robed figures carries a scroll in her hand to signify the solemnity of her mission. She represents the rule of the law. Next to her is a figure cradling a model of the earth in her left hand, while in her right is a forward-facing mirror such that citizens may perceive the image in truth as they chart a future in which all collectively benefit. She represents the universal truths of science.

Indeed, there is no physical place more metaphoric of the intellectual journey that led me to produce this work than under their protective gazes, who are aptly symbolic of two women in particular to whom I owe the most immense thanks. To Bartha and Jill, my life is forever changed by the liberty you actively protected for me to explore the depths of our discipline; the courage you instilled in me through enriching my mind; the trust you placed in me towards furthering our pursuits of contributing to a more just world vis-à-vis responsible scientific progress; and lastly, perhaps most transformative, your unwavering belief in me as a scholar and a human.

To my parents whose love and sacrifice are the foundations upon which my happiness and life successes are built. You are beacons of integrity and humility that guide me in the face of seemingly impossible decisions, and who I aspire to emulate in every sense. To Stephano, who shows me daily what it means to live a life of dedication, purpose and compassion. You are my greatest teacher. Drs. Carolyn Ells and Amalia Issa, I cannot thank you enough for your guidance through each phase of this endeavor, for reading countless drafts of this thesis, and for lending calming words of wisdom. To Dr. Eugene Bereza, whose mentorship, friendship and deep devotion to preserving the human condition is my shining example for higher education in our discipline.

I want to express my deepest gratitude to all my colleagues at the Centre of Genomics and Policy and Department of Family Medicine for your continuous support, holiday invitations and Montreal adventures you shared with me over the seven years we spent together. I am so very grateful for the study spaces I frequented in order to write these pages, and to all those who made these spaces feel like a home away from home. Namely my friends at Gentile and Melk cafes, thank you for the writing refuges you provided and for keeping me in the highest of spirits and caffeination!

I am especially thankful for the funding support of the following throughout my doctorate career, without which my accomplishments would not have been possible: the Canadian Institutes of Health Vanier Canada Graduate Scholarship, an award that singularly changed the course of my academic trajectory; Genome Canada; Canadian Chair in Law and Medicine; the Canadian Institute of Health Services and Policy Research; Canadian Institute for Child and Youth Health; Pink in the City and the Hellenic Scholarship Federation; Canadian Bioethics Society; and the Public Population Project in Genetics and Society (P^3G). I am deeply humbled by the guidance and support of the abovementioned, and the many more who I know I have not listed for a second dissertation-length volume would be needed to express my thanks to them.

Equipped with the wisdom and strengths these individuals fostered in me, I am confident my mirror of truth shall continuously face forward in all future pursuits within and outside the academy.

Dedication

For all children without a diagnosis,

who deserve to benefit from the fruits of scientific knowledge.

Statement of originality and contribution of authors

The following describes the significance of the interrelated studies planned in this thesis in terms of advancing theory, practice, and filling a knowledge gap at the intersection of bioethics, data governance and pediatrics. The informational feedback loops driving clinical progress in the genomics-enabled learning health system rely on the production, use and exchange of data, including from children. The policies and practices guiding proportionate governance of such production, access and exchange are, however, markedly limited in the pediatric genomics space. Despite the research-care nexus that genomics-enabled learning health systems afford, the respective ethical-legal traditions circumscribing appropriate oversight of data sharing in clinical research and care remain separate and distinct. The need for policy-practice coherence in genomic data sharing can be accentuated when involving populations such as children, from whom data may require special protections. Absent understanding the ethical-legal bases upon which responsible pediatric data sharing should rest, present and future children may not reap the benefits of a healthcare system that continuous 'learns' from the production, use and exchange of genomic and associated clinical data.

This thesis makes an original contribution to empirical bioethics in pediatrics by interrogating the policies, practices and principles guiding responsible sharing of genomic and associated clinical data internationally and in Canada. It first identifies the ethical-legal, social and scientific considerations thereof, paying special attention to the roles of research ethics, and other data governance mechanisms implicated in the pediatric data-intensive sciences. The thesis then applies the principles, procedures and policies of responsible data sharing to validate an ethical-legal framework for pediatric genomics in Canada. Such a framework is one policy pillar upon which genomics-enabled learning health systems can build to improve standards of care for Canadian children and their families.

As Dereli et al. aptly describe, studies at the intersection of emerging data technologies and society ought more to be concerned with understanding rather than predicting:

> Big data is, in essence, a call to be cognizant that scientific knowledge is not only a product of technology and evidence but also uncertainty (known unknowns) and ignorance (unknown unknowns), not to mention politics attendant to human values and scientific practice. For too long, modernity has been preoccupied with the idea that uncertainty can be eliminated from science, and thus has prescribed a rigid line dividing scientific facts and human values. (Dereli et al. 2014, 50)

This thesis attempts to arrive at Dereli's proposed understanding, notably how responsible genomic and associated clinical data sharing is framed and practiced in pediatrics. It makes theoretical contributions to understanding the governance-practice links that enable genomic and associated clinical data sharing, and moreover what normative ethical-legal factors strengthen—or alternatively problematize—this link where children are involved. Qualitative data centered on the value systems, priorities and interests among those charged with stewarding children's genomic data have not yet been systematically collected, until now, with respect to how they influence the development of responsible data sharing policies for Canadians. When the ethical-legal norms that bind responsible governance and practices of data sharing align, the science of pediatric genomics can advance in directions that are responsive to the publics that responsible governance aims to serve.

The contributions afforded through understanding the governance-practice links of data sharing are complemented in this thesis by its contributions to advancing practice. Developing an ethical-legal framework based on conceptions of responsible sharing advances the field in two original ways. In the most general sense, a framework circumscribes the peoples, places and tasks that define scopes of practice. The framework developed in this thesis superimposes, for the first time, ethical-legal norms onto the people, places and things that do the work of responsible data sharing involving children in Canada. A commitment to proportionality, rather than protectionism guided the normative stances to genomic data production, analysis and exchange the proposed framework espouses in this thesis. While other frameworks have been developed with similarly proportionate goals for policy development in mind (Global Alliance for Genomics and Health, n.d.), none have an explicit pediatric focus. That the proposed framework is supported empirically as well as experientially makes it evidence-based, yet practically inspired from the clinical and research narratives of Canadian data sharing stakeholders. As such, the framework uniquely reflects norms accepted in the literature with jurisdictional specificity built in where appropriate to the Canadian context based on empirical findings.

Lastly, this thesis furthers the academic discipline of health services and policy research in adding to its methodological compendium. It combined, for the first time, a systematic review of reasons with policy Delphi methods to study the policy-practice links of genomic data sharing involving children. Not traditionally rooted in health services and policy research, empirical bioethics can offer critical lenses through which to unveil sociotechnical value conflicts, support anticipatory

governance theory, and inform research agendas for emerging technologies according to public priorities.

The pages contained herein are organized in a manuscript-based format that includes 4 stand-alone manuscripts plus one methods chapter (Chapter 3) and discussion (Chapter 6). V. Rahimzadeh is either the sole, or first-listed author on all published and submitted manuscripts that comprise this thesis. Funding to support both interrelated studies, as well as publications fees for the 2 published manuscripts was provided by the Vanier Canada Graduate Scholarship (CIHR#358258); Canada Research Chair in Law and Medicine; and Precision Medicine Policy Network. The following agencies supported academic conference attendances where preliminary results were presented and where peer feedback was obtained: Institutes for Community Support Travel awards (CIHR#335517, CIHR#363843); Network of Applied Medical Genetics (RMGA) Travel Fellowship; American Association for the Advancement of Science Student Poster Prize; Pink in the City on behalf of the Hellenic Scholarship Federation.

The introductory chapter is a single-authored book chapter published in *Progress and Challenges in Precision Medicine* (pp. 171-185) by Academic Press in 2017. All background research, concepts, research design, data collection/analysis, manuscript drafts and conclusions were based solely on the ideas of V. Rahimzadeh with input regarding relevant literatures and clarifying arguments from thesis advisors G. Bartlett and B.M. Knoppers. The initial Key Implications for Data Sharing (KIDS) framework elaborated in Chapter 4 was published in the *Journal of the American Medical Association Pediatrics* in early 2018. All co-authors of this *JAMA Pediatrics* piece comprised a key informant committee of the Paediatric Task Team of the Global Alliance for Genomics and Health. Members of the key informant committee deliberated on, and helped refine the initial suite of policy position statements in the KIDS Framework, which was subsequently validated in the Canadian context in the policy Delphi study (Chapter 5). V. Rahimzadeh led in the organization of the key informant meeting during the 4th Plenary of the Global Alliance for Genomics and Health in Vancouver, British Columbia; all note taking and data collection during the meeting; analysis of meeting results and consensus points; coordination of committee feedback; and preparation of all drafts of the manuscript prior to publication. The systematic review of reasons in Chapter 2, as well as results from the policy Delphi in Chapter 5 have been submitted for publication in peer-reviewed bioethics and pediatric clinical medicine journals.

Preface to Chapter 1 Introduction [Manuscript 1 published as a book chapter in *Progress and Challenges in Precision Medicine]*

Chapter 1 explores proportionate data governance approaches that facilitate the integration of genomics and the data ecosystems that power them. It asks whether special ethical distinctions that apply to vulnerable populations like children in research should apply to secondary use of children's genomic and associated clinical data in the pediatric data-intensive sciences (DIS). It concludes that data sharing fulfills dual ethical and scientific imperatives, introduces three intersecting responsibilities of data stewardship towards the data's source, process and impact. The typologies of vulnerability as applied to interrogating the ethics of participation in research can be a useful normative starting point from which to determine whether these same distinctions can be applied to sharing genomic data. Proposing that data sharing in the pediatric DIS should be pursuant to proportionality rather than protectionism coheres broadly with the child's right to an open future and promotion of bests interests, among other principles that are summarized in greater depth in Chapter 2.

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Chapter 9

Sharing Outside the Sandbox? The Child's Right to an Open Data Sharing Future in Genomics and Personalized Medicine

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1. INTRODUCTION

Consortia-based research in genomics has revolutionized the ways in which data are generated, stored, and shared to answer contemporary biomedical questions (Ekins et al., 2014; Kao et al., 2014; National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease, 2011; Shaikh et al., 2014; Stephens et al., 2015). It has furthermore reconfigured the movements and trajectories of data that once were confined to siloed laboratories conducting "lone science" (Knoppers, 2013). This has also been the case for genomic research involving children (Evans, 2013; Janeway et al., 2013; Wilfond and Ross, 2009), where international consortia rely on the sharing of linked genotypic and phenotypic data to make sound associations between the genome and etiologies of (childhood) disease (Higdon et al., 2015; Hochedlinger, 2015; Janeway et al., 2013). Data sharing in pediatrics risks falling victim to prohibitive-masked-as-protectionist policies and practices that for many years contributed to near exclusion of children from clinical research in the wake of research abuses at the Willowbrook School and others (Diekema, 2006).

Anticipatory governance of data sharing is therefore needed to strike a proportionate balance between protection and open science that undergirds the successful integration of precision

medicine for improving pediatric health. This chapter interrogates the ethics of sharing genomic data in what is increasingly referred to as the pediatric data-intensive sciences (DIS).[i] It provides a brief overview of the emergence of special protections for children (and other vulnerable groups) in research and discusses whether the same ethical distinctions apply in pediatric DIS. It lastly defends the sharing of pediatric genomic data with proportionate protections in fulfillment of both the child's right to an open future and human right to benefit from the advancement of science.

2. CHILDREN IN RESEARCH

The notion of special protections for certain research populations was first introduced in the World Medical Association Declaration of Helsinki in 1964 (World Medical Association, 1964). It identified children, among others, as a research population easily exploitable in medical research due to their inability to provide informed consent (International Bioethics Committee, 2011). Since its introduction in the Declaration of Helsinki, vulnerability in research has been a focal point of ethics in research and care. Vulnerability in research can result from social marginalization, poverty, cognitive impairment, or cognitive (under)development to name a few, and can impose undue pressure and influence on decision-making. Bamford clarifies how an enhanced philosophical understanding of vulnerability is needed if research ethics boards (REBs) are to mitigate the aforementioned consequences, especially in health services research (Bamford, 2014). Lange et al. further categorize sources and temporalities of vulnerability that are pertinent to research ethics: inherent, situational, and pathogenic. Inherent vulnerability refers to a level of dependency on others that is an "inescapable element of the human condition" (Lange et al., 2013, p. 336), while situational vulnerability can be temporary or ongoing and is socially, politically, or economically context-specific. In contrast, pathogenic vulnerability can "arise from dysfunctional social or personal relationships... often characterized by injustice, persecution or political violence. Sometimes pathogenic vulnerabilities arise when social policies aimed at protecting against situational vulnerabilities have the perverse effect of generating new vulnerabilities" (Lange et al., 2013, p. 336).

According to Lange's distinctions, the source of children's vulnerability in research can most appropriately be classified as situational. In most jurisdictions, children's (in)ability to consent is temporal upon reaching the legal age of majority; in others it is determined by assessing competency

[i] The data-intensive sciences (DIS) are embedded in what Hey et al. (2009) first described as the Fourth Paradigm of Science. DIS can be broadly defined as fields of inquiry, which generate, collect, store, and share massive volumes of data characterized by their variety, value, and veracity.

(Fernandez & Canadian Pediatrics Society, 2008)[ii]. Children without surrogate decision-makers can, however, be excluded from research meant to better understand pediatric health and/or provide improved health services. Exclusion from research, in turn, creates knowledge gaps that prevent health improvements in this population as a whole (Kipnis, 2003). In general, full and informed consent requires understanding of the study procedures, its anticipated risks, and appreciation for both the current and future implications of research participation. Parents, legal guardians or, in some circumstances, the State are charged with consenting on behalf of the child in accordance with the child's best interests (Binik et al., 2011; United Nations Convention on the Rights of the Child, 1989). Research with children, and indeed with situationally vulnerable groups generally, therefore raise an ethical tension. Children warrant special ethical protections as a result of their situational vulnerability. They should not, however, be categorically excluded from research that anticipates the contribution of new knowledge that could improve their health and wellbeing. Although this tension is not new, the types of risks genomic data sharing poses to children and the approaches research ethics review committees employ to minimize them are unique. From this tension furthermore emerges a series of important policy questions for children's participation in DIS research typified by the -omics disciplines, and their subsequent rights as beneficiaries of the knowledge generated therein. First, should the sharing of genomic data derived from children—like research participation—warrant stricter protection than other forms of data sharing? Do the same vulnerability categories attributable to children as physical bodies in the research process also apply to their data? These questions will be taken up in latter sections of this chapter.

3. A CHANGING LANDSCAPE FOR PEDIATRIC RESEARCH PARTICIPATION

Sequencing the first human genome marked an evolution in the conduct of biomedical research (Collins et al., 2003; Lander et al., 2001), including in pediatrics (Downing et al., 2012; Wilfond and Ross, 2009). Biomedical research has also increasingly become a data-intensive venture (Lynch, 2008) that requires collaboration between researchers and institutions (Ekins et al., 2014; Hudson and Collins, 2015; Kaye et al., 2009; Khoury et al., 2013; Knoppers et al., 2011; Kosseim et al., 2014). The massive amounts of data required to adequately power sound statistical associations between the genome and (childhood) diseases substantiate this need to collaborate. As such, sequence data is the engine of genomics, while data sharing the vehicle by which bench-to-bedside translation (Green

[ii] See also Article 21 of the Civil Code of Quebec (Civil Code of Québec, n.d.).

et al., 2011) proceeds[iii]. Data, when systematically collected and analyzed pursuant to a proposed research question can also be considered essential activities that create an ecology of learning in healthcare (Faden et al., 2013). The exercise of sharing data varies widely across disciplines, purposes, and societies. The conception of data sharing adopted in this chapter follows from the definition proposed by Tenopir et al. in the context of DIS including genomic research: "Data sharing includes the deposition and preservation of data; however, it is primarily associated with providing access for use and reuse of data" (Tenopir et al., 2011, p. e21101).

The authors further describe general advantages of data sharing in a research context specifically, and which may include:

- re-analysis of data helps verify results data, which is a key part of the scientific process;
- different interpretations or approaches to existing data contribute to scientific progress, especially in an interdisciplinary setting;
- well-managed, long-term preservation helps retain data integrity;
  when data is available, (re-)collection of data is minimized; thus, use of resources is optimized;
  data availability provides safeguards against misconduct related to data fabrication and falsification; and
- replication studies serve as training tools for new generations of researchers (Tenopir et al., 2011).

Research ethics review is an important landmark on this translational continuum (Zawati et al., 2015) that sees the mobilization of new biomedical knowledge into improved standards of care, for example. In this regard, sharing research data fulfills dual imperatives in the translational endeavor: (i) a scientific imperative, which arises from the need to determine underlying genetic determinants of disease; and (ii) an ethical imperative to generate the anticipated benefits of the research for which the balancing of risks to (pediatric) research participants in part rests. For REBs and data access committees (DAC), genomics raises chiefly informational risks (Rothstein, 2015). These risks require that REBs ensure protections that are DIS-oriented among others (Ogbogu et al., 2014), such as privacy, confidentiality, and interoperability particularly for the purposes of secondary use of data. In contrast to historical conceptions of risk upon which early research ethics guidelines were premised, informational risks associated with DIS are defining a new typology of research participation that engenders unique ethical considerations (Jamal et al., 2014; Mathews and Jamal, 2014). In pediatric oncology clinical trials, for example, children's participation may be typified by

[iii] The conceptual link between the ethical and scientific imperatives of data sharing is summarized by Bull, Roberts, and Parker in Table 1 (Bull et al., 2015). According to recent evidence, the time between bench and bedside is on average 17 years (Morris et al., 2011).

research procedures inflicted directly on the physical body— such as drawing blood, or exposure to experimental drugs with unknown toxicity to name a few. The imposition of research procedures associated with DIS research, in contrast, are instead performed on material data that is experientially divorced from the physical body. Some studies suggest that such disembodiment pacifies the (hyper)precaution that may often contribute to children's exclusion from clinical research. Other studies have found that parents in fact make more restrictive decisions in sharing their children's data than individually consenting adults (Burstein et al., 2014; McGuire et al., 2011b) participating in similar studies. The following section outlines how policy models of research ethics review, alongside data protection law, are implicated in the data-sharing endeavor for the pediatric DIS community.

4. THE RESEARCH ETHICS REVIEW PROCESS AND IMPLICATIONS FOR DATA SHARING

It is reasonable to start from a bioethical posture that posits the special protection of children's research data follows from the special protections they warrant when participating in research. REBs are charged with ensuring the anticipated benefits of research participation, either directly for the individual child or indirectly for children in a similar group, do not outweigh foreseeable risks (Canadian Institutes of Health Research Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada, 2014; Council for International Organization of Medical Sciences, 2002; Department of Health and Human Services, 2009; International Bioethics Committee, 2011). Because the broader societal benefits of genomic research are largely contingent upon sharing and analyzing genomic data (Harris and Wyndham, 2015), REBs should also be attuned to how studies propose to responsibly carry out such sharing. The degree of intra- and international collaboration characteristic of genomic research involving children, however, raises additional challenges. These include the paucity of data sharing guidelines as they specifically relate to sharing pediatric data, as well as existing procedural mechanisms of ethics approval that have, until recently, adopted an institution-by-institution approach.

The latter is especially problematic when collaborative genomic research spans across multiple sites (Needham et al., 2015) as they often do. Various models of centralized ethics approval mechanisms pursuant to the principle of mutual recognition (Zawati et al., 2015) have been suggested to facilitate data sharing in part by enhancing the consistency of the informed consent process (Brownstein et al., 2015). Despite this, only recently have the procedural issues and research

delays attributable to multisite ethics review (Al-Shahi Salman et al., 2014) translated into health policy action to reform ethics approval (Department of Homeland Security Department of Agriculture Department of Energy Department of Commerce Agency for International Development Department of Justice Department of Labor Department of Defense Department of Education Department of Veterans Affairs, 2015; He bert and Saginur, 2009).

A number of Canadian provinces (e.g. AB, BC, QC, ON) and pediatric research networks (Maternal Infant Child Youth Network, MICYRN), for instance, are in the process of centralizing ethics review for multisite studies (MICYRN, n.d.). That is, one REB accepts the decisions of other REBs under certain agreements (Dove et al., 2013; Knoppers, 2014). Centralization may better complement the volume and nature of multisite collaboration that DIS typify (Dove et al., 2013). It furthermore aims to more proportionately respond to the informational, rather than physical risks DIS poses to children and their data. Proposals to pilot centralized models between REBs have been initiated (Lavery et al., 2005; Rahimzadeh and Knoppers, 2016), but few are pediatric-specific (Margolis et al., 2013) or explicitly address the regulatory and ethical challenges of sharing pediatric research data (McGuire et al., 2011a). Little empirical research to date quantifies the resource demands of existing ethics review procedures for pediatric infrastructure research (He bert and Saginur, 2009), nor what impact they have on data sharing. This intersection between empirical bioethics and health policy is an area of unmet need to realize the promises of genomic medicine in pediatrics. The subsequent section of this chapter proposes a set of ethical considerations and rationales for what responsible sharing of data could look like in pediatric DIS.

5. SHARING OUTSIDE THE SANDBOX

"Data sharing is a shared responsibility," noted the International Committee of Medical Journal Editors in a recent position statement on sharing clinical trial data (Taichman et al., 2016). Other international organizations (Global Alliance for Genomics and Health, n.d.), government bodies (National Institutes of Health, 2003), and research consortia (Dyke and Hubbard, 2011; Hochedlinger, 2015; Joly et al., 2012; Jones et al., 2012) have also made fervent calls for a more concerted data sharing agenda within the biomedical research community (Gewin, 2016). Legal scholars have defended a broader data sharing man- date from a human rights perspective (Knoppers et al., 2014; Knoppers and Joly, 2007), drawing from twin rights outlined in Article 27 of the Universal Declaration of Human Rights to substantiate their position:

[1] Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts, and to share in scientific advancement and its benefits.

[2] Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary, or artistic production of which he is the author. General Assembly of the United Nations (1948)

Related rights protected under Article 12 of the UN Convention on the Rights of the Child that endorse freedom of expression and participation in civic life for children (United Nations Convention on the Rights of the Child, 1989) further support a pro data sharing position. Dena Davis' thesis on a child's right to an open future (Davis, 2009) provides an additional lens through which to examine how data sharing can be implicit in this future. Although originally invoked as an argument against directed procreation in absolute terms, such as parental sex selection and trait enhancement, the right to an open future might also encompass one where society actively shapes a future that enables research to improve children's lives. Put simply, if biomedical research is the cornerstone of biomedical progress, then that which enhances the biomedical research endeavor—responsible data sharing in this case—should be facilitated.

This logic necessarily creates an accompanying duty to actualize it. Those involved in the research endeavor, including researchers, funders, policy makers and others would have a responsibility to enhance the infrastructural and cultural foundations of data sharing in DIS. More frequently in bioethics, debate arises in operationalizing ethical ideals. If data sharing is considered an ethical and scientific imperative in genomics, then what is required such that data may be shared more widely?[iv] Furthermore, how (if at all) should research data involving children be treated distinctly than from adults? A recent empirical study puts these issues into sharp relief. In a randomized control study on data sharing in the United States, experimental informed consent documents were used to gauge participants' propensity to share their genomic data. Study participants were either children enrolled, or parents of children enrolled in six national genomic studies investigating: pediatric brain cancer, pediatric brain controls, pediatric autism, adult/pediatric epilepsy, adult/pediatric liver cancer, and adult pancreatic cancer (McGuire et al., 2011b). Parents in the study chose one of three data access mechanisms outlined in the informed consent document: open access (public release), controlled access (restricted release), or no access other than the

[iv] Indeed, some research has attempted to shed light on why researchers are reluctant to share data. Prominent reasons for the lack of sharing include fear that future researchers could undermine author conclusions, discover errors in the dataset, and instigate publication wars (Savage and Vickers, 2009).

investigators of the current study (no release). The researchers found that parents of prospective participants made more restrictive data sharing decisions when consenting on behalf of their children, opting for "no release" of data approximately four times more than adults consenting for themselves. Their findings revealed parents were most concerned about the future, as yet unspecified informational risks posed by genomic data sharing. In contrast, adult participants were chiefly concerned about privacy and discrimination.[v]

The following sections will deconstruct the responsibilities inherent in mitigating these risks. The ways in which such responsibilities are distributed among genomic data producers, custodians and users help to lay a practical groundwork for responsible sharing of genomic data in pediatric DIS.

5.1 Responsibility to the Data Source

There are few other information sources that can be as uniquely identifying as genetic information. Genetic information is used to determine forensic culpability (Stajano et al., 2008), dictate pharmaceutical prescribing (Phillips et al., 2001), and find lost relatives (Royal et al., 2010) to name but a few applications. Some scholars have proposed that genetic information is even fostering novel conceptions of identity formation and connection (Knoppers and Ozdemir, 2014; Widdows, 2012). In this regard, genomic and other forms of health-related data can be conceived as material manifestations of individuals' identity available for consumption and analysis under a scientific gaze. When sensitive data derived from children is the subject of this gaze, the identifiable features inherent their genomic data can further reinforce children's situational vulnerability. Parents consent on behalf of their children to share their genomic data and, as a result take part in shaping their child's "open future". Given the ethical significance of genomic data as an identity proxy, researchers who act as consumers and custodians of this data have a responsibility to respect its source.

Others have suggested that the ethical imperative to share children's genomic data may be accentuated as a result of the means through which the data was generated. One example is sharing data from studies involving terminally ill children where mortality rates are the primary end points (Cheah et al., 2015), or other similar studies which are unlikely to be repeated but yield valuable contributions to new knowledge. In these circumstances, it can be argued that sharing research data

[v] The study was conducted just before passage of comprehensive legislation against genetic discrimination in the United States, the Genetic Information Nondiscrimination Act

may be the primary means of respecting the contributions of research participants and promoting justice among the populations through distributing research benefits.

5.2 Responsibility to the Data Process

A responsibility to the data process by nature animates the responsibility to the data source. Here too Tenopir et al. offer a useful map of the data trajectory in the research process, whereby "the data lifecycle cannot be considered independently from research lifecycle" (Tenopir et al., 2011, p. e21101). The data process commences with simulation/experimentation/observation, proceeds to data management, and ends with analysis and sharing. Specific ethical–legal considerations are tailored to each landmark of this process, not the least of which include data privacy. Privacy laws vary considerably by jurisdiction. They converge, however, on the importance of consent for disclosure of identifiable information and the ways in which a specific data environment (Heeney et al., 2011) may lend itself to potential breeches. Access to research and patient level data is in large part determined by the nature and type of data to be shared. Sophisticated data access arrangements, coding software and secured cloud storage platforms have been developed to protect both individual patient and aggregated data housed in data repositories such as biobanks. While open and controlled-access agreements correspond to the least and most restrictive levels on the data access continuum, respectively (Fortin et al., 2011), a middle-tiered access framework has also been proposed for sharing some forms identifiable patient data (Dyke et al., 2016). Data access arrangements often stipulate that data can only be shared with bona fide researchers who have obtained specific credentials. A responsibility to the data process may also encompass making data interoperable, or usable for secondary research purposes. Data interoperability is achieved through standardizing data collection procedures, for instance, that allow for systematic comparison across datasets and enable secondary use.

5.3 Responsibility to the Data Impact

Sharing genomic data maximizes two utilities, scientific and social, in the pediatric DIS enterprise. The scientific utility of research data, like that generated in biomedical research and other DIS disciplines not in its materiality, but rather its ability to answer research questions. The social utility of genomic data is realized when these scientific answers can translate into improved health outcomes or healthcare delivery. The relationship between social and scientific utility of research data gives rise to a third responsibility to the data impact. Underutilization of biobanked

data/samples underscores the significance of this third responsibility best. While there have been many studies to explore public perceptions of biobanks, there is comparably little in the bioethics and health policy literature exploring the ethics of underutilizing biobank data (Cadigan et al., 2014; Henderson et al., 2013).

As Cadigan et al. rightly identify, underutilization is an affront to the altruistic premise upon which participants donate their samples/data. The authors argue, "Optimizing utilization is a professional ethical imperative in the same way that appropriate citation and peer review are ethical matters: it reflects the communal nature of the scientific process and common goal to advance reliable knowledge for its own sake" (Cadigan et al., 2014, p. 739). Underutilization of biobank samples/data can trivialize the act of donation if we accept that biobank donation is a "morally significant act" (Tomlinson, 2013). This is particularly true for donors who report altruism toward the health of future patients as one principal reason for donation (Tomlinson et al., 2015), and that donors expect at a minimum their donations will be used to advance science. The ethical responsibility to the data impact—which necessarily invokes justice principles that support the inclusion of children in research and opportunity to benefit from science—can be accentuated in the pediatric DIS context considering the unique data source and data process responsibilities outlined earlier.

6. CONCLUSION

This chapter situated contemporary ethical challenges of data sharing in the pediatric DIS within the historical narrative of special protections for research involving children. Data sharing fulfills dual ethical and scientific imperatives in the postgenomic era, that in turn gives rise to three primary responsibilities of genomic data producers, custodians and users. The typologies of vulnerability used to nuance the involvement of "vulnerable" participants in research such as children and incompetent adults can be a useful starting point for interrogating whether these same categorical distinctions can be applied to genomic research data. This chapter moreover proposed that three intersectional responsibilities pursuant to ethical proportionality (Wright et al., 2015), rather than protectionism should ethically motivate data sharing in the pediatric DIS community. This coheres with the child's right to an open future implicit in shaping medical progress through both scientific means and societal priority setting.

Future research and complementary approaches to ethics governance are needed, however, to provide practical guidance for the data sharing ideals proposed herein. Involving stakeholders

associated with data contribution, production and use is essential to developing internationally interoperable data sharing policies that also respect local values. This is to say nothing of the infrastructural capacities in IT, data analytics, and computing needed to allow for the responsible exchange of data between and among researchers internationally. The revolution in genomic big data effectively opened the door for precision and personalized medicine. It is the responsibility of those within the pediatric DIS community to ensure this door—metaphoric of the sociotechnical futures imagined for children in the post genomic era—remains open.

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Following from the knowledge gaps identified in Chapter 1, the overarching aim of this thesis is to provide practical ethical-legal guidance that enables responsible sharing of genomic and associated clinical data involving children in Canada. Two research questions guided the thesis in achieving this aim by combining a systematic review of reasons with a three-round policy Delphi study.

The thesis first asks, **I**) *what ethical, legal, and social and scientific factors enable responsible genomic and associated data sharing involving children?* The clinical conditions for which data sharing and translation of genomic discoveries hold some of the most promising clinical benefits often present early in life. The introductory chapter explored **a)** proportionate data governance approaches that facilitate the integration of genomics in delivering pediatric precision health and debated whether special ethical distinctions that apply to vulnerable populations like children should apply to secondary use of children's genomic and associated clinical data in the pediatric data-intensive sciences (DIS) . Balancing promotion and protection of children's data to harness these clinical opportunities requires alignment between ethics governance/policy and data sharing practices in the data-intensive disciplines like genomics. The policy-practice coherence of pediatric data sharing with normative ethical standards for research and clinical care are posed to the empirical and grey literature in a systematic review of reasons reported in Chapter 2. The review considers **b**) normative ethical principles, policies and practices that constitute 'responsible' sharing of genomic and associated clinical data when this data are derived from pediatric patient-participants. From the synthesis of reasons used to answer research question **I**), a second question was posed to investigate **II**) *how do Canadian pediatricians, genomic researchers, ethicists and bioethical scholars prioritize the ethical-legal, social and scientific factors of genomic and associated clinical data sharing involving children in Canada?* The thesis then maps the principles, procedures and policies discovered in **a)** and **b**) onto **c)** an ethical-legal framework for responsible sharing of children's genomic and associated clinical data in Canada. The thesis objectives pursuant to research question **II** are to assess the proposed ethical-legal framework for its relative importance, feasibility, desirability and confidence, as well as to identify consensus and dissention of the framework as it applies to the Canadian pediatric genomics context, specifically. In turn, the policy Delphi offers implementation recommendations and directions for future applied bioethics or health policy research that extends the data policy negotiation processes that panelists involved in this study initiate in the pediatric genomics space.

Preface to Chapter 2 [Manuscript 2 to be published in an empirical bioethics or pediatric clinical journal]

The introductory chapter introduced proportionate data governance approaches that facilitate the integration of genomics towards delivering pediatric precision health. It explored whether special ethical distinctions that apply to vulnerable populations like children in research should apply to secondary use of children's genomic and associated clinical data in the pediatric data-intensive sciences (DIS).

The systematic review of reasons reported in Chapter 2 landscapes the grey as well as the empirical data sharing literature to construct the normative bases of responsible data sharing in pediatrics. The combination of literatures draws from the broadest array of reason-based sources where ethical-legal themes on pediatric data sharing can be captured. In doing so, the review answers research question **I** of this thesis: *what ethical, legal, and social and scientific factors enable responsible genomic and associated data sharing children?* The synthesis of reasons presented in Chapter 2 lays the ethical-legal foundation upon which a Canadian policy framework for pediatric data sharing is negotiated in a policy Delphi study of Canadian pediatricians, researchers and bioethics scholars (Chapters 4 & 5).

Lead author VR conducted the literature search with the support of a reference librarian at the McGill University Department of Family Medicine, screened all articles, performed the quality appraisal and conducted the thematic content analysis on all retained records using NVivo 11 software. Supervisor GB acted as the second independent reviewer during the screening process. GB and BMK reviewed the codes and approved the final manuscript as it appears in Chapter 2.

CHAPTER 2 LITERATURE REVIEW [Manuscript 2]

A Systematic Review of Reasons for Responsible Genomic and Associated Clinical Data Sharing Involving Children: The Bioethical Golden Rule?

V. Rahimzadeh, B.M. Knoppers, G. Bartlett

Abstract

Data of enormous volumes, veracities and validities are needed to power statistically sound associations between the human genome and disease, of which many emerge in the earliest years of life. Twin imperatives emerge from these needs—one scientific, one ethical—to substantiate how and why genomic and associated clinical data involving children more widely, securely and efficiently. To achieve both imperatives, approaches to responsible data sharing should strive to proportionately protect, rather than categorically exclude children from opportunities to benefit from the advances that concerted data sharing makes possible. This systematic review searched the empirical and grey literature indexed in MedLine, BIOSIS, Scopus, and Web of Science literature for policies and practices supporting responsible reuse, re-analysis, re-combination and repurpose of children's genomic and associated clinical data. All empirical studies using qualitative, quantitative and/or mixed methods were included and appraised for quality using the MMAT. We included: commentaries, editorials or position statements; conference proceedings; professional organization reports; and international or professional guidelines if they were published in English between 2002 and 2017. We reviewed 151 records for reasons given to support both 'why' and 'how' children's genomic and associated clinical data should be shared. We thematically coded 563 unique Reason Mentions that were then synthesized to inform a draft framework on what practices and policies constitute 'responsible' genomic and associated clinical data sharing in pediatrics.

1. Introduction

Translating discoveries in precision medicine to achieve improved individual- and population-level health outcomes necessitates broad sharing of genomic and associated clinical data. Such sharing is especially pertinent during childhood, when many Mendelian and other heritable genetic conditions

first present and are clinically actionable. Twin imperatives emerge from this clinical translational endeavor—one scientific and one ethical—and which calls for modeling proportionate data governance and security to fulfill both imperatives. First, statistically sound associations between the human genome and (childhood) disease are only possible with the availability of data of increasing volumes, veracities and validities. Support for improved standards of care and positive risk-benefit balances in part rest on the anticipated associations that linking genomic and associated clinical data potentiate for children. These imperatives subsequently give rise to three primary responsibilities of genomic data producers, custodians and users (V Rahimzadeh et al. 2018). Normative and procedural tensions, however, challenge responsible governance in data sharing practice. In this review, pediatric data (sharing) refers to the

> broad exchange of genome sequencing data and associated clinical descriptors from an individual child, either as part of clinical care or research. Pediatric genomic and associated clinical data may include, but are not limited to, specific characterization of genetic variants and their associated clinical phenotypes, all whole-genome and whole-exome variants, and links to detailed genotypic and phenotypic profiles of pediatric patients and their unaffected family members (V Rahimzadeh et al. 2018).

The combined sensitivity of, and as-yet undetermined future uses for pediatric data lead to ethical-legal ambiguities in determining appropriate levels of protection. The sensitivity of children's genomic and associated clinical data increases with its potential identifiability. As data become more easily identifiable as a result of sequence data linkage with electronic medical records, for example, so too must data management and securities enhance in sophistication. Linking children's genomic and associated clinical data have already led to significant advancements in understanding phenotypic and genotypic bases of childhood diseases, especially in oncology (Downing et al. 2012), rare genetic disease (Boycott et al. 2014) and autism (Mefford, Batshaw, and Hoffman 2012), to name but a few examples.

Vulnerabilities in, and of data sharing in pediatric genomics

Children's inability to consent to most research and clinical care decisions that may require their linked genomic and associated clinical data underpins their status as a population in circumstances of vulnerability whose data may warrant special protections. Kipnis (2003) describes seven such circumstances that arise in pediatric research that are likewise useful for describing the types and sources of vulnerability children may experience in sharing their data:

1. Incapacitational: Does the C-S lack the capacity to deliberate about and decide whether to participate in the study?
2. Juridic: Is the C-S liable to the authority of others who may have an independent interest in that participation?
3. Deferential: Is the C-S given to patterns of deferential behavior that may mask an underlying unwillingness to participate?
4. Social: Does the C-S belong to a group whose rights and interests have been socially disvalued?
5. Situational: Is the C-S in a situation in which medical exigency prevents the education and deliberation needed to decide whether to participate in the study?
6. Medical: Has the C-S been selected, in part, because of the presence of a serious health-related condition for which there are no satisfactory remedies?
7. Allocational: Is the C-S or proxy lacking in subjectively important social goods that will be provided as a consequence of participation in research? (Kipnis 2003)

Like Kipnis does in his analysis, incapacitational and juridic vulnerabilities can be considered together. Children lack the legal capacity to be sure, and often the maturity to deliberate on decisions to share their data, thereby relying on parents or other guardians to decide in their stead. Juridic subordination to parental authority in sharing the child's genomic and associated clinical data is thus borne from incapacitational vulnerabilities children experience when unable to appreciate the long- and short-term benefits and risks of data sharing for themselves. Deferential vulnerability is also relevant insofar as children comply with data sharing decisions made by trusted adults without challenging the rationales of those recommendations in substantive ways. Data sharing is not unlike other clinical decision-making processes in this respect, especially when data are shared explicitly for diagnostic purposes, or to confirm optimal treatment approaches or as a quality of care measure in the event the condition is exceedingly rare, to propose just several examples. The potentially negative ramifications of deferential vulnerability may be most pronounced when future adult makes an informed decision later in life to withdraw data contributed when they were a child, but may be unable to if this data is anonymized or aggregated.

The normative starting point for improving ethical-legal policies and practices for sharing children's data adopted in this thesis is a rights-based one. That is, children's participatory rights and respect for their personhood motivate sharing their data more widely, accessibly and securely. Given this orientation, responsible data sharing envisioned herein is poised to be a solution to, rather than an exacerbation of social vulnerabilities that arise from exclusionary policies and practices in clinical research. The latter are instantiated in protectionist research regulations that have historically limited

children's opportunities to benefit from scientific projects, rights that are protected under Article 27 of the United Nations Declaration. Not all children may access these benefits equitably, however. Diagnostic genome-wide sequencing may not be available or accessible to all children for whom it could be medically beneficial. Clinical use of children's genomic data presumes scientific infrastructures are in place to produce it, and health services available to act on it. These human and material resource constraints are practical realities in resource-poor settings that in turn produce social vulnerabilities experienced by some, but not all children. For similar reasons, allocational vulnerabilities may only be relevant where children's data are exchanged for subjectively necessary social goods. While not illegal to buy and sell medical information, its commodification should be cautioned.

Perhaps most relevant to sharing children's data are the situational and medical vulnerabilities that near constant evolution in measurable informational risks and genomic etiologies of pediatric disease, respectively, give rise. Unknown biological understanding of most rare genetic diseases and their optimal treatments, for example, are the clinical realities that can underscore children's medical vulnerability in deciding whether to share their data. Data sharing may be the only avenue for identifying the few other patients in the world that harbor the same genetic mutations, giving treating physicians an opportunity to learn the phenotypic and genotypic bases of the condition from which to treat future children. Medical vulnerability can be compounded by situational vulnerability in this case, where the longitudinal risks to distributing linked genomic and clinical information are uncertain. One potential dilemma data sharing presents to parents in this instance is one in which the prospect of enhancing clinical best interests requires additional risks to children's informational security, albeit minimal.

Governance and oversight

In research contexts, research ethics review committees (RECs) and data access committees (DACs) constitute two oversight bodies charged with balancing the benefits of information sharing with the informational risks such sharing and secondary data uses afford. In clinical contexts, relevant information privacy laws govern what, and when such data can be shared and with whom e.g. HIPAA, PIPEDA. Privacy and security concerns can be accentuated for children in light of their consent-related vulnerabilities (Freedman, Fuks, and Weijer 1993), particularly when the use of children's data for future, as-yet unspecified purposes are the norm rather than the exception in the data-intensive sciences (O'Neill 2003; Kyle Bertram Brothers 2011; Kristien Hens et al. 2013).

Sharing linked genotypic and phenotypic data that may originate in either research or clinical contexts, however, may afford the only opportunity for accurate diagnosis or to determine the most effective treatments.

It is primarily under these clinical circumstances, and those related to sharing genomic data from banked biospecimens involving children that this systematic review of reasons considers in depth. Although data involving children and other vulnerable populations such as incompetent adults deserve special protections (Rahimzadeh et al. 2017), disproportionately restrictive data access policies may in fact thwart data-driven innovations used to inform evidence-based standards of care. To this end, we contend that responsible data governance in pediatric genomics relies on a proportionate balance between data protection and opportunities for innovation made possible through concerted data sharing. Sparse empirical attention has been paid, however, to understanding what constitutes 'responsible' sharing from ethical, legal, social and scientific standpoints when data involves pediatric populations.

A systematic review of reasons according to Sofaer and Strech (2012) with quality appraisal of empirical studies was conducted in order to fill this aforementioned knowledge gap. Systematic reviews of reason "take into account the specific conceptual and practical challenges of empirical bioethics," (Strech, Synofzik, and Marckmann 2008) while preserving the systematicity associated with traditional reviews. This method of review makes ethical-legal argumentation the primary outcome of interest when synthesizing the literature. Such reviews furthermore enable reviewers to search for and contextualize the varied types of knowledge that reason-based literatures produce, making it particularly conducive to answering multidisciplinary questions of bioethical inquiry meant to inform ethics policy and practice.

This systematic review posed the following research questions of the literature, *Which reasons have been given to support the view that children's genomic and associated clinical data should be shared?* Early analyses of the Reason Mentions suggested that no publication explicitly rejected data sharing outright. In contention, rather, was when, and under what circumstances such sharing could be considered ethically responsible from philosophical, technical and scientific endpoints. Only one reason we analyzed argued for an exceptionally high threshold for genomic testing and subsequent sharing of this data: "If whole genome sequencing to identify preventable diseases or SNPs or haplotypes associated with drug responsiveness does occur, the child's DNA should be discarded afterwards and genomic information erased or stringently protected. If protective measures are not feasible, a decision will have to be made whether to genotype them at all"(Robertson 2003).

A second, complimentary review question was therefore posed to both the empirical and grey literature in order to map the ethical-legal arguments that researchers, clinicians, bioethicists and others used to support the 4Rs[vi] of data sharing: *How are these reasons used to inform responsible reuse, reanalysis, repurpose and recombination (4R) of children's genomic and associated clinical data in policy and practice?*

2. Literature Search Strategy

The review team searched the empirical and grey literature indexed in MedLine, BIOSIS, Scopus, and Web of Science with the support of a reference librarian at the McGill University Department of Family Medicine. All empirical studies using qualitative, quantitative and/or mixed methods were included and quality appraised using the MMAT (Pace et al. 2012). We also included: commentaries, editorials or position statements; conference proceedings; professional organization reports; and international or professional guidelines if they were published in English between 2002 (year the Human Genome Project was publicly announced) and 2017. The detailed search strategy can be found in **Appendix A**. A document e.g. empirical study, guideline or data sharing SOP was included if it:

(I) Discussed ethical, legal, social (ELSI) or scientific reasons supporting reuse, reanalysis, recombination, or repurposing data from genome/exome sequencing of children

(II) The sharing of genomic or associated clinical data involved patients aged 0-18 years old (neonates to the age of majority in most jurisdictions)

(III) The sharing of genomic or associated clinical data was derived either in the context of pediatric clinical research or care, and conformed to our definition of pediatric data sharing described above.

[vi] For the purposes of our review, we adopt Collman and Matei's (2016) definitions of the 4Rs (Collman and Matei 2016): **Reanalysis**— Refers to developing new lines of inquiry and techniques for extracting new information from already collected source data; **Recombination**— Refers to developing new (meta) information from constituent data sets made available to the investigator. Recombining data potentially enables re-identification of individuals from data that contains no specific identifiers or has been intentionally stripped of identifiers; **Repurpose**— Refers to taking data originally collected for a specific purpose in a specific domain and analyzing them for unrelated purposes in a domain other than their domain of origin. In addition to the questions posed by reusing data, repurposing big data poses questions about the legitimacy of analyzing data acquired under one privacy context and employing it in a different privacy context; **Reuse**— Reuse refers to taking data originally collected for a specific scientific purpose and using them again for comparable purposes in comparable domains.

Condition (I) covers ELSI reasons that constitute responsible genomic data reuse, reanalysis, repurpose and recombination involving children without explicitly endorsing or rejecting particular data sharing mechanisms, platforms or tools. Reasons mentioned under condition (II) restrict the scope of data sharing to pediatric populations, specifically, and to ELSI reasons invoked that promote special protections required when handling pediatric data therein. Given genomic and associated clinical data collected under the auspices of research may also have clinical significance—and vice versa—we employed condition (III) to reflect the diversity in genomic data provenance in the pediatric context.

Records were excluded if pediatric data sharing was discussed only in relation to the return of incidental findings/individual research results or disclosing results of newborn screening. The breadth of recent systematic reviews (Mackley et al. 2017; Bertier et al. 2017) and rigorous empirical research (McGowan et al. 2018; Burke et al. 2013; Holm 2017; Bishop, Strong, and Dimmock 2017; Petersen et al. 2017; Driessnack and Gallo 2011) on these themes informed this exclusion criterion. Our review furthermore aims to better understand elective data sharing when, say, it is encouraged for diagnostic purposes or to advance pediatric genomic medicine generally, rather than as a public health mandate like newborn screening. For similar reasons, we also excluded technical papers where data interoperability or security measures were proposed without discussion of the ethical, legal or social considerations motivating these measures [vii].

Lead author VR conducted the thematic content analysis on all retained articles and policy documents using the NVivo 11 software. To produce a preliminary coding scheme, VR scanned the document for all mentions of "data shar*", "pediatric," "ethic*" to categorize whether the ethical-legal arguments answered either the *What* and/or our *How* review question. This initial step was necessary because the review topic does not lend itself neatly to binary positions e.g. analysis of arguments for or against data sharing[viii] that inspired the first published systematic review of reasons (Sofaer and Strech 2011). Karpowicz et al. adopted a more qualitative analytical approach by coding reason mentions as either foundational or consequential based on the substantive purpose the arguments served in the ethical-legal issue under study(Karpowicz, Bell, and Racine 2016).

When piloting Karpowicz's coding approach in our review, we observed that foundational

[vii] While return of incidental or secondary findings is considered a form of data sharing, this review of reasons focused on 4R sharing outside the individual care nucleus. Similarly, newborn screening programs may imply 4R sharing, yet are obligatory forms of data collection and management mandated by the State and under the auspices of public health.

[viii] Indeed, only 1 of 151 records advocated for the position that strict limitations be placed on the generation of, and continued access to genomic sequencing data involving children (Robertson 2003).

arguments were almost exclusively found in policy documents, guidelines and laws, whereas empirical studies, commentaries and other position statements chiefly invoked consequential arguments to support data sharing. Moreover, we found both forward and reverse rhetorical strategies were used to support why data should be shared; meaning, authors articulated the positive consequences of sharing, as well as the negative consequences of *not* sharing pediatric data. We found the latter was invoked most often in records discussing the types of data sharing benefits anticipated (see section 3.3). While we did not categorize the arguments we analyzed based on foundationalist and consequentialist arguments as did Karpowicz et al., we developed a coding schema that differentiated arguments into 'what' and 'how' arguments corresponding to the two review questions. **Table 2** provides a full coding guide we used to contextualize all broad and narrow Reason Mentions pursuant to these review questions.

3. Search Results

After removing duplicates, we screened 1779 unique records based on title and abstract and reviewed 457 full texts for inclusion. A total of 118 documents were retained from the literature search, the bibliographies and in-text references of which we then hand searched for any normative guidance documents(s) e.g. policies, guidelines, conventions the authors used to support their reasons. The snowball search resulted in an additional 33 records. Eight records were international policies related to: research ethics (2) and the human rights of children (1) and data sharing policies (5); 3 records were special reports on the topic of data sharing involving children, and 21 were empirical articles (**Figure 1**).

4. Record characteristics

Included records were characterized by their

- Publication type
- Content type
- Journal field
- Context in which pediatric data sharing was primarily discussed

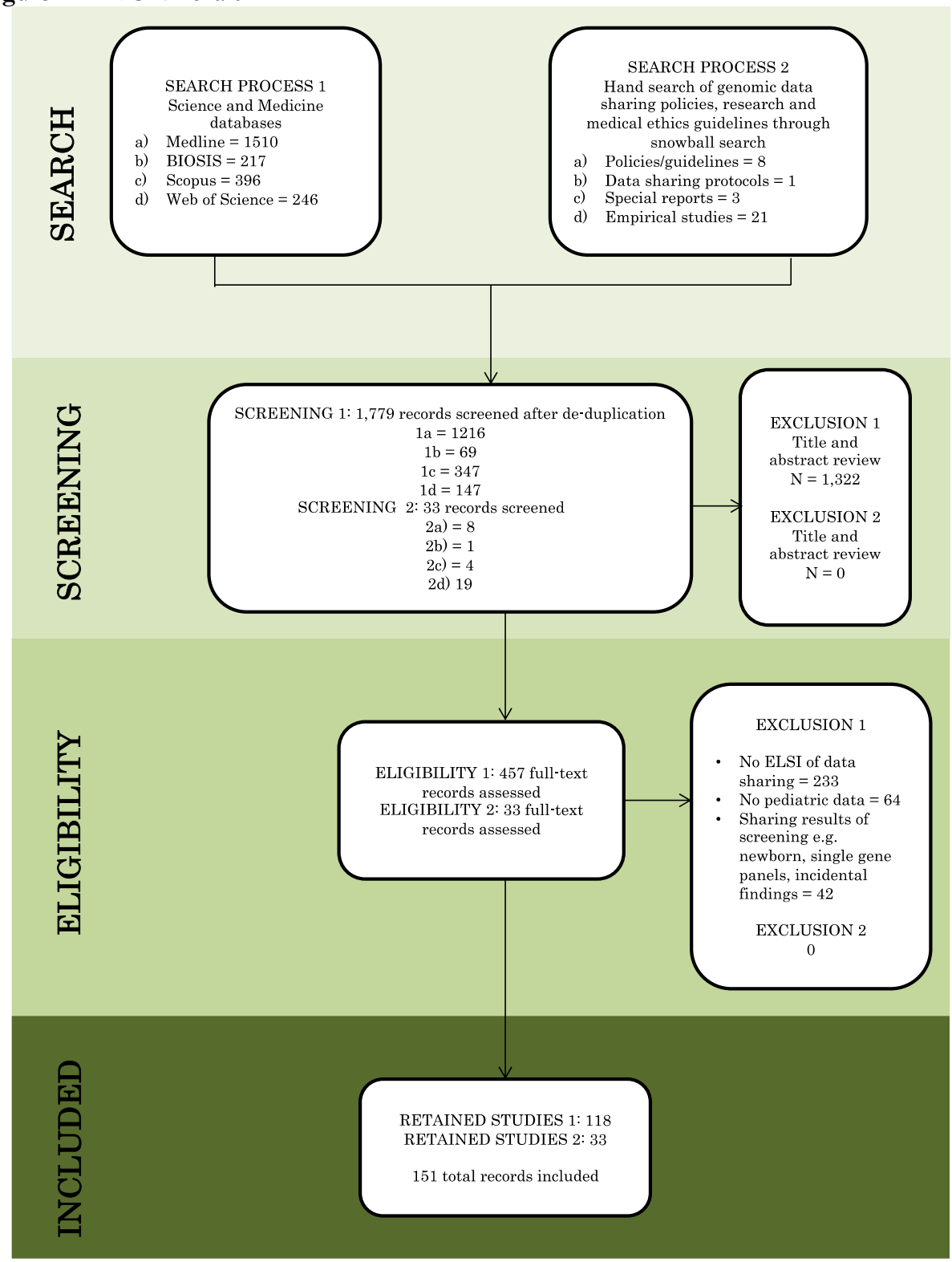
Sixty-five (43%) of included records discussed data sharing in an ethical-legal commentary/opinion piece, while 27 (18%) discussed ethical-legal considerations for sharing children's data as part of a formal pediatric data sharing program or consortia. All 43 empirical studies retained were critically appraised using the Mixed Methods Appraisal Tool (MMAT); 39 (94%) earned a MMAT score of 0.75

or higher. A summary table of publication characteristics is provided in **Table 1**. Four publications present results from 2 empirical studies (Burstein et al. 2014; Amy L McGuire et al. 2011; K Hens et al. 2009b; K Hens et al. 2009a). Nearly half (49%) of all included records for which a publication year was available were released between 2013 and 2017 inclusive.

Table 1. Publication characteristics

	N (%) of publications
Publication Type	
Peer reviewed article	125 (82)
Book section	3 (1.9)
Report	4 (2.6)
Journal published letters	4 (2.6)
Press release	4 (2.6)
Conference proceedings	2 (1.3)
Guideline/policy	9 (5.9)
Content Type	
Empirical study	43 (28)
Commentary or opinion piece	65 (43)
Data sharing guideline/policy	5 (3.3)
Data sharing SOP	27 (18)
International convention or national guideline	5 (3.3)
Professional guideline	1 (0.6)
Regulation	2 (1.3)
Field of journal for 139 peer reviewed articles, published letters and news headlines	
Medicine	41 (27)
Bioethics	17 (12)
Health policy/law	6 (4.3)
Public Health	10 (7.2)
Genetics/genomics	42 (30)
Social science	6 (4.3)
General science	12 (8)
Nursing	2 (1.4)
Informatics	4 (3)
Published in 2016 (most prolific year)	19 (14)
Region of publication or policy/guideline/law	
North America	93
Europe	43
Middle East	1
Asia	3
New Zealand/Australia	3
Africa	4
Other (international)	4

Figure 1—PRISMA chart



5. Identifying Reason Mentions

We reviewed 151 records for reasons given to support both 'why' and 'how' a child's genomic and associated clinical data should be shared. We identified 10 Broad, and 7 Narrow Types of Reasons related to the former, and 8 Broad and 18 Narrow reasons for the latter (**Table 2**). We thematically coded 563 unique Reason Mentions according to Types across all 151 records included in the review. Maximizing clinical and scientific utility of children's data, and modalities of data sharing consent had the highest number of Broad Reason Mentions pursuant to our 'why' and 'how' review questions, 19 and 27, respectively. The right to recontact/reconsent to continued data use at the age of majority (34) and the scope of parental authority to consent broadly to data sharing (29) garnered the highest number of narrow Reason mentions for both review questions. Eight (32%) of narrow Types of Reason, and 4 (22%) of broad Types of Reason had fewer than 5 reason mentions, respectively.

Table 2. Coding guide for broad and narrow reason mentions by review question

*Coding guide for publications discussing reasons **why** children's genomic and associated clinical data should be shared [No. of reason mentions] {122}*	*Coding guide for publications discussing **how** children's genomic and associated clinical data should be shared [No. of reason mentions] {441}*
1. To enhance the prospect of direct and indirect benefits to individual, as well as other pediatric patients i. Direct clinical benefits for the patient [7] ii. Indirect benefits to other, as well as future children [12] • Indirect benefits justified on the basis of solidarity [1] iii. Direct and indirect benefits to patient(s) [8] **2. To advance pediatric medicine generally [12]** i. To improve diagnostic yields [4] ii. To develop new drug therapies [5] **3. To support the learning healthcare system** [1] **4. To maximize the clinical and**	**11. Modalities of data sharing consent [29]** i. Broad consent for unspecified, future use [11] ii. Children's assent and shared decision making [27] iii. Scope of parental authority to provide broad consent to sharing, including for future unspecified use [29] • Joint parental consent [2] • Posthumous consent [1] iv. Consent waivers to secondary/future data use [8] iv. Right to re-contact/re-consent for continued data use at the age of majority [35] • Ethics committee to determine re-contact responsibility [7] • Opt in/out to continued data use [12] v. Implications of data sharing for the family [5]

scientific utility of children's data [19]
    i. To improve statistical power and sample size [14]
5. **To prevent data waste** [5]
6. **To mobilize public health responses** [3]
7. **To encourage research collaboration** [13]
8. **To enable verification and reproducibility of genomic results** [6]
9. **To minimize patient burdens and risks by not duplicating data collection** [4]
10. **To fulfill a duty to share** [8]

12. **Responsible data management [9]**
    i. Via mechanisms of mutual accountability for data sharers and users [3]
    ii. Via interoperability and ease of use [13]
        - Need for a shared data lexicon to support interoperability [4]
    iii. Role of institutions in data management [5]
        - Need for harmonized norms [6]
    iv. Clarification of data ownership [7]
13. **Responsible data protection [18]**
    i. Special protections for genomic data [9]
    ii. Compliance with applicable data protection law [14]
    iii. Appropriate data de-identification [25]
        - Technical strategies for data-de-identification to comply with ethical-legal guidelines [10]
        - Data linkage and implications for re-identifiability [19]
14. **Responsible data access [10]**
    i. Via data use(r) restrictions [29]
15. **Balancing benefits with informational risks [17]**
    i. Physicians and investigators are responsible for balancing benefits and risks [1]
    ii. Evaluating risks based on current evidence [5]
        - Minimal risk standard [12]
    iii. Risks related to loss of privacy [12]
        - via unauthorized third-party access [15]
        - via genetic discrimination [3]
        - uncertain risks related to secondary/ future use [4]
16. **Continuing education and stakeholder outreach [13]**
17. **Incentivization and appropriate attribution for data sharers [6]**
18. **Enhancing patient willingness and trust [10]**
    i. Methods to enhance trust and

	willingness to share [7]

5.1 Reasons '*why*' share genomic and clinically associated data?

We identified 122 Reason Mentions for why pediatric genomic and associated clinical data should be shared. These mentions were thematically organized into 10 Broad, and 7 Narrow Types of Reasons (**Table 2**). Broad Reasons related to anticipated data sharing benefits were subdivided to distinguish among three discreet types of benefits we identified—direct (7), indirect (12) and both indirect and direct (8)— and the anticipated beneficiaries of those benefits—individual patients or other/future children with similar health conditions. One Reason Mention considered the merits of data sharing synonymous with the clinical decision to pursue genomic testing itself(Robertson 2003). That is, the author argued sharing genomic and associated clinical data should only be pursued when in the immediate clinical interests of the child. This was the only Reason Mention interpreted to be against any type of data sharing unless expected to result in a direct benefit.

Indeed, the notion of the child's best interests was often raised conjointly with the types and prospects of (in)direct benefits anticipated, particularly when data was derived clinically. Six Reason Mentions invoked the argument that data sharing should enhance the prospect of direct clinical benefits to the child, several of which provide empirical findings from public perception studies to support that parents believe data sharing should result in direct clinical benefits to their child. Two of these 6 Reason Mentions reported actual direct benefits to participating in data sharing programs, including improved diagnosis and targeted treatment decisions based on the child's genomic profile (Sijmons, Van Langen, and Sijmons 2011; Giannuzzi et al. 2017).

Ten broad Reason Mentions justified data sharing based on the prospect of generating indirect benefits to other and future children, including 1 narrow Reason that based this justification on the solidarity principle. This finding is noteworthy in that the prospect of benefit beyond the immediate clinical interests of the individual data donor is, according to parents and families surveyed in the literature, a formidable consideration in making decisions to allow for secondary data use. Three Reason Mentions (Tozzo, Pegoraro, and Caenazzo 2010; K Hens et al. 2013; Anderson and Merry 2009) likened data sharing to an altruistic act for which "contributing to the public interest or to the common good [prevails] on the direct individual consequences of the donation"(Tozzo, Pegoraro, and Caenazzo 2010).

Eight Reason Mentions made claims that a direct benefit is too high a threshold upon which to justify sharing children's data (Kaufman et al. 2008; Harris et al. 2012; Kristien Hens, Lévesque, and Dierickx 2011; Murad et al. 2017; Lunshof 2013; J Kaiser 2006; Mascalzoni, Paradiso, and Hansson 2014a), and that the prospect of indirect benefits to other and future children are more reasonable expectations. These Reason Mentions considered the implications of data sharing significantly upstream of the clinical translational process—in contexts such as pediatric biobanking— where "direct benefit is never the primary aim…and the restriction 'direct benefit' is too stringent"(Kristien Hens, Lévesque, and Dierickx 2011). Hens et al., maintain this indirect benefit argument is central to the ethics of secondary use in pediatric biobanking context across seven publications we analyzed (K Hens et al. 2011; K Hens et al. 2009a; K. Hens et al. 2010; K Hens et al. 2013; Kristien Hens et al. 2011; Kristien Hens, Wright, and Dierickx 2009; K Hens et al. 2009b). Indeed, the prospect of indirect direct to other and future children are permissible conditions under which children should be invited to participate in research using their data according to international conventions (World Medical Association 2013; Council for International Organization of Medical Sciences 2002). We found 3 of 8 Reason Mentions invoked converse arguments to support the prospect of both direct and indirect clinical benefits. The authors warned of the consequences that *not* sharing children's data could invite: "[researchers] should not prohibit the publication of sequencing information that could save lives,"(Lunshof 2013) that they could subsequently let "children down by not [sharing data]"(Jocelyn Kaiser 2006) and that not sharing health records and biospecimens could impede "the only "chance that others have (whether affected or not) within a biological family to receive better-quality healthcare"(Mascalzoni, Paradiso, and Hansson 2014a).

Maximizing the scientific and clinical utility of children's data was cited as the most frequent Broad Reason why pediatric data should be shared (19), followed by the need to improve sample sizes to further enhance the informational utility drawn from sharing children's data (13 narrow Reason Mentions). Seven records discussed data linkage, specifically, as a primary way to improve variant interpretation and thereby inform clinical action during childhood (Bowdin et al. 2016; Lloyd et al. 2015; Bertier et al. 2017; Sijmons, Van Langen, and Sijmons 2011; Beale et al. 2015a; Kristien Hens et al. 2009; Jiang et al. 2009; Brett and Deary 2014). Five broad Reason Mentions supported the idea that sharing enhances the quality and analysis of pediatric data by enabling verification/reproducibility of shared data, with the added benefit of preventing data waste (4 Broad Reason mentions). In addition to supporting the scientific value of data verification and

reproducibility, authors argued that sharing data previously collected from children also avoids imposing additional informational risks. Three records made this link explicitly, asserting that sharing should be encouraged when data are "special or that would be difficult or expensive to duplicate"(Birmingham and Doyle 2009).

The relative rarity of some pediatric conditions, coupled with the statistical power demands of making sound associations between genotype and phenotype were together offered as primary reasons for data sharing that facilitate data sharing (see Mccormack et al. 2013; Anonymous 2016) for example). Of the 13 broad Reason Mentions for sharing data to encourage research collaboration, authors argued that genomic understanding of specific childhood disease and prevalence rested on data linkage across institutions (Rapp 2016; J. H. Holland 2006; Mascalzoni, Paradiso, and Hansson 2014a; J. K. Fisher, Bromley, and Mansfield, n.d.). The inter-institutional collaboration achieved via a "pediatric clinical study network would be an excellent test case for raising public awareness regarding the value of global collaboration"(Mary A. Majumder, Cook-Deegan, and McGuire 2016). The inspiration to expand collaboration from local, to international data sharing was also observed in the Autism Speaks' Autism Genome Project, which grew to become an "international consortium of over 120 scientists from 50 institutions worldwide that pools resources for their genetic analyses"(Lajonchere and Consortium 2010). This corroborates our earlier assertion that data linkage is critical to assessing both the genotypic and phenotypic associations of interest underlying childhood diseases.

The Types of Reasons we analyzed often used pediatric rare disease, and other undiagnosed genetic conditions as exemplar cases for which the above 'why' reasons for sharing genomic and associated clinical data were especially pronounced. Our finding is unsurprising as the rare disease research community is among the most vocal in advocating for broader sharing of data involving both adults and children (Boycott et al. 2013; Svenstrup, Jørgensen, and Winther 2015; Reuter et al. 2018; Lacaze et al. 2017). Rare disease research and care, distinct from other fields of pediatric research and care, was also treated as a special case for determining what constitutes responsible data protection and privacy(Bartha M. Knoppers 2013; Sijmons, Van Langen, and Sijmons 2011) (see section 3.45).

The combined broad (10) and narrow (7) Reasons we identified cohere with recently published ethical frameworks that instantiate why data sharing should be an ethical obligation of scientists, primarily because sharing enables, among others, data replication, scientific progress, ensure public trust and fulfill human rights(Duke and Porter 2013). Actualizing the clinical and

broader scientific benefits of data sharing mentioned in the records we reviewed, implicates research and clinical ethics, data governance and health information technology. Our analysis of arguments pursuant to our secondary, 'how' review question indeed highlights this interplay and are discussed at length below.

5.2 Reasons '*how*' should genomic and clinical data be shared?

We categorized 441 total Reason Mentions related to *how* children's genomic and associated clinical data should be shared into 8 Broad, and 25 Narrow Reasons (**Table 2**). By far the highest number of total Broad and narrow Reason Mentions of any reason category centered on the theme of consent (166). We identified 69 Broad Reasons that discussed evaluating informational risks, while 47 concerned responsible data management, data access (39) and data protection (95). The involvement of community stakeholder groups towards establishing responsible data sharing practices constituted three additional broad Reasons, namely the importance of community outreach and continued education (13 Reason Mentions), enhancing stakeholder willingness and trust in the data sharing enterprise (17 Reason Mentions) as well as incentivizing data sharing vis-à-vis appropriate attribution (6 Reason mentions). We summarize the corresponding arguments and recommendations when provided below.

5.21 Modalities of informed consent

Authors debated most about the modalities of the informed consent process relative all other themes considered in this review, what information this process should entail, and who is authorized to provide such consent to continued use of children's genomic and associated clinical. The complexity of the informed consent process stemmed in part form ambiguity around parents' authority to consent broadly to sharing their child's data, and for how long this authority should be recognized. Records discussed whether broad, as opposed to explicit, consent should be permitted for secondary/future reuse (11 Narrow Reason mentions); whether broad consent falls within the normative scope of parental authority (29 narrow Reason Mentions); and when consent waivers are permissible for secondary use (8 narrow Reason Mentions).

While the limits of broad consent can be jurisdictionally- or even institutionally-specific, the records we reviewed generally accepted that it involves a one-time permission on behalf of patients or their surrogates to reuse data or samples already collected for future research purposes that may

or may not be related to those motivating the original collection(Riggs et al. 2018; Sanderson et al. 2017). Broad consent is particularly advantageous for enabling learning activities in the genomics-enabled learning health system, where biobanked samples can be used for longitudinal analyses, for example, or for updating clinical databases that enable clinicians to recontact patients when a variant's pathogenicity gets reclassified(Beachy, Olson, and Berger 2015). Two reason mentions confirm these advantages, specifically(Manolio et al. 2007; Bertier et al. 2017). While 3 Reason Mentions supported explicit consent for secondary data use where possible (Kranendonk, Hennekam, and Ploem 2017; A L McGuire et al. 2011; Joseph et al. 2008), 24 Reasons Mentions supported how alternative consent models, including broad, dynamic and notification with opt-out could reasonably satisfy the normative requirements[ix] underlying informed consent.

Irrespective of the consent model adopted, 27 narrow Reason Mentions underscored the importance of children's involvement in developmentally appropriate capacities, namely by obtaining their assent. The right to recontact led the consent debates regarding secondary and continued use of children's data and samples (35 narrow Reason Mentions). Debates centered on when data users should be required, if at all, to obtain legal consent from individuals for continued use of their data collected when they were a child. Only one record argued for mandatory re-contact on the basis that the "parent's authorization on behalf of the child should no longer prevail when the child has capacity to make an independent choice" (Samuël et al. 2008). The majority of records rather strongly suggested that data users attempt to re-contact children (now adults) when logistically possible, or else obtain approval from a research ethics board to waive any re-contact requirements (7 narrow Reason Mentions).

Four records we reviewed were associated with a scholarly exchange regarding the consent specificities of sharing biobanked samples and data involving children. The original article, authored by Gurwitz et al. (2009), appeared as a Policy Forum piece in the journal Science. In it, the authors defended a relatively conservative approach to sharing pediatric data by current standards, arguing

> In contrast to policies for disease-specific research, we feel that an overhaul is needed for the collection and distribution policies of DNA samples and data from children that have been included in population biobanks. We propose that population biobanks continue to collect, store, and analyze children's DNA and phenotypic data with the appropriate authorization by parents or guardians, but that they may not make these DNA samples (or individual genetic sequence data) accessible outside the biobank until donors are recontacted as adults and give their own informed consent.

[ix] Consent should be voluntary, informed and free of coercion.

They go on to assert that adopting a no continued use policy until recontact at the age of majority would "marginally affect" research and only in the "short term"(Gurwitz et al. 2009a). Three letters to the editor submitted in response to Gurwitz et al strongly critiqued the above recommendation (Hansson and Maschke 2009; K B Brothers and Clayton 2009; Kristien Hens, Wright, and Dierickx 2009). Authors of the editorial letters argued, among others things, waiting to use children's data and samples until their ability to consent "will delay the advancement of important scientific discoveries and run counter to the altruistic reasons for participation in research studies"(Kristien Hens, Wright, and Dierickx 2009). Doing so places "too much weight on consent" argue others, and that instead the "potential harm posed by data sharing can be mitigated by limiting the data to be shared, removing identifiable elements, and maintaining thorough oversight"(K B Brothers and Clayton 2009). Read in conversation with each other, the 4 records support an overall conclusion that re-contact at the age of majority is preferred so as to respect the evolved decision-making capacities of now-adults whose parents consented to contributing their data as children. The original authors clarified this in a subsequent response (Gurwitz et al. 2009b). But secondary and continued use of this data should be contingent on recontact considering the significant logistical barriers this could impose on researchers, to say nothing of the actual research that could be thwarted without access to this data.

5.23 Responsible Data Management

We refer to data management here as the comprehensive collection of administrative processes and practices that follow data from its initial acquisition to storage, update and distribution. The records we synthesized also interpreted data management to include administrative tasks that render datasets interoperable for sharing across institutions, and sometimes international borders to, among other reasons, inform clinical care or research questions. The charge to responsibly manage data falls to institutional data custodians or management committees (9 broad Reason Mentions). We identified two approaches institutions and data custodians used to achieve this: via mechanisms of mutual accountability for both data sharers and users mutually accountable for the data (3 narrow Reason Mentions) and by improving interoperability and ease of use (13 narrow Reason Mentions). Four Reason Mentions cited explicitly the need for a standardized lexicon to facilitate such interoperable sharing, much like that which was endorsed by the Global Alliance for Genomics and Health (2016).

Clarifying data ownership was an additional responsibility of data managers according to 7 narrow Reason Mentions we identified. An equal number of Reason Mentions (3) supported that data ownership lies with patients, as institutions. Arguments supporting the former argued that data derived from biospecimens are an extension of the patient's physical body and warrants their right to control what happens to this data. Others reasoned that institutions which expend resources to maintain samples/data ultimately own its contents as well as any benefits derived therein.

5.24 Responsible Data Protection

The Types of Reasons pursuant to what constitutes responsible protections for children's linked data were both technical as well as ethical-legal. Only one Reason Mention made the argument that children's data categorically requires more stringent data protections beyond those required for someone will full capacity to consent: "If whole genome sequencing to identify preventable diseases or SNPs or haplotypes associated with drug responsiveness does occur, the child's DNA should be discarded afterwards and genomic information erased or stringently protected"(Robertson 2003). Rather, 9 narrow Reason Mentions made the claim that genetic/genomic data warrants special protections categorically and irrespective of the data contributor, especially when linked with other clinical data sources given the inherently identifiable nature of such data.

Fourteen narrow Reason Mentions made the claim that responsible data protection complies with applicable data protection law/guidelines[x]. Generally, data protections were considered proportionate to the sensitivities of the (linked) data shared, the intended purposes for the data being shared, and the likelihood of unauthorized re-identification(Kyle B Brothers et al. 2014; C. B. Fisher, Harrington McCarthy, and Harrington 2013; Kristien Hens et al. 2011; Scholtens et al. 2015; SACHRP 2018; Kyle Bertram Brothers 2011). Authors argued that these protection responsibilities rest with professionals(World Medical Association 2013) or data stewards in research contexts(Manolio et al. 2007). It is worth noting that privacy and data protection were oftentimes discussed together despite the conceptual ethical and legal differences distinguishing them (see for example (Gostin 1995)). We identified that privacy-preserving themes characterized the Types of Reasons invoked to support responsible pediatric data protection, while privacy-diminishing themes

[x] All laws/guidelines named in these narrow Reason Mentions were included as official records in this review e.g. HIPAA, NHGRI Data Sharing Policy, Common Rule

more closely associated with Types of Reasons characterizing immediate and future informational risks to the child as a result of data sharing.

The most-mentioned broad Reason (25) supporting responsible data protection involved data de-identification. Under this broad Reason, 10 narrow Reason Mentions discussed the technical de-identification strategies that not purport not only to satisfy regulatory and ethical mandates to protect children's data, but also preserves its scientific and clinical utility. Although linking multiple datasets together was perceived to enhance the likelihood of re-identifiability (19 narrow Reason Mentions), such linkage was overwhelmingly endorsed with adequate data governance and oversight infrastructures in place(Canadian Institutes of Health Research Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada. 2014; Lea 2013; C. B. Fisher, Harrington McCarthy, and Harrington 2013; Lloyd et al. 2015; Tevah Platt et al. 2014; Driessnack and Gallo 2011; Giesbertz, Bredenoord, and van Delden 2015; Heeney et al. 2011; Suresh et al. 2005; Mascalzoni, Paradiso, and Hansson 2014b; M A Majumder et al. 2017; Ebner et al. 2016; Wjst 2010; Said et al. 2017; Manolio et al. 2007; Brett and Deary 2014). Our finding is consistent with ongoing initiatives to improve technical backends(Wan et al. 2017; Decouchant et al. 2018; Humbert et al. 2017) as well as one patent application(Hubaux et al. 2018) that too are motivated by strengthening this protection-utility ratio.

Lastly, 4 of the broad Reason Mentions under data de-identification were pediatric data sharing protocols that described why and how adopting contemporary encryption technologies to de-identify data was appropriate, 7 other protocols discussed coding or pseudo-anonymization to strip data of specific identifiers. Also of note was that the earliest publication included in this review identifying potential privacy risks associated with sharing (2005) preceded most publications describing privacy-preserving solutions by 14 years. This trend at least partially indicates the pace of computational advancements in privacy protection since sequencing the human genome.

Responsible Data Access

The terms of ethically responsible access to shared genomic and clinical data was contingent on the type of pediatric data shared—e.g. anonymized, coded—where data were being deposited and by whom e.g. researchers/clinicians in a clinical variant database. By far controlled access via user restrictions was the most-mentioned narrow Reason (29) supporting responsible access to identifiable, or coded data. Seven records invoking this narrow Reason described the role of data access committees, data use agreements and other confidentiality agreements to manage controlled access requests(Pediatric Imaging, Neurocognition, and Genetics (PING) Study 2011; Ries,

LeGrandeur, and Caulfield 2010; Birmingham and Doyle 2009; Wjst 2010; J. K. Fisher, Bromley, and Mansfield 2016; Jernigan et al. 2016; Manolio et al. 2007), and 3 records named ethics review boards as primary arbiters of data access (Pinto et al. 2015; Mccabe and Mccabe 2011; Tindana et al. 2012).

5.24 Benefits and Risks

Seventeen broad Reason Mentions described responsible sharing as a balance of benefits and risks between two competing priorities. We found three distinct types of balances under this broad Type of Reason. The most frequently discussed balance (12 Reason Mentions) was between fulfilling ethical-legal obligations to protect children and contributing new scientific knowledge that benefits pediatric medicine (Bertier et al. 2017; Manhas et al. 2016; A L McGuire et al. 2011; Burstein et al. 2014; Magnus and Health 2015; Kristien Hens et al. 2011; T Platt et al. 2017; C. B. Fisher, Harrington McCarthy, and Harrington 2013; Kristien Hens, Wright, and Dierickx 2009; Dowty and Korff 2009; Manolio et al. 2007); the balance between respect for individual versus public rights(Ahrens et al. 2006; Petrini et al. 2012), and between preserving confidentiality and right to data access(Jean Golding 2009; Nooner et al. 2012) were both raised in 2 Reason Mentions. One Reason Mention discussed a balance between society and commercial benefits when entering into public-private partnerships with the pharmaceutical industry. The authors contended that sharing pediatric data to expedite drug development—specifically for rare disease—and protecting the commercial interests of the pharmaceutical partners was considered carefully by members of a scientific steering committee for a large rare disease clinical databank(Mccormack et al. 2013).

The vast majority of records we analyzed implied that assessing the anticipated benefits and risks such to strike a favorable balance is complicated when they are unknown at the time of data contribution(Dowty and Korff 2009; Bertier et al. 2017; Manhas et al. 2016; Amy L. McGuire et al. 2011; Tevah Platt et al. 2014; Burstein et al. 2014; C. B. Fisher, Harrington McCarthy, and Harrington 2013; Kristien Hens, Wright, and Dierickx 2009; Kristien Hens et al. 2011; Magnus and Health 2015; Nooner et al. 2012; Ahrens et al. 2006; Anderson and Merry 2009; J Golding 2009; Lunshof 2013; Manolio et al. 2007; Petrini et al. 2012; Kristien Hens, Lévesque, and Dierickx 2011). Of the hypothetical risks anticipated, threats to loss of privacy were discussed generally (12 narrow Reason Mentions). Unauthorized data access by third parties was the most-mentioned narrow Reason for loss of privacy (15) followed by genetic discrimination (3). While not inconsequential(Christofides and O'Doherty 2016), the risks of sharing genomic data involving

children are generally considered minimal based on the minimal risk standard (12 narrow Reason Mentions), especially when data are de-identified(C. B. Fisher, Harrington McCarthy, and Harrington 2013; M A Majumder et al. 2017). Current policies and practices of responsible data sharing that aim to minimize these risks are being developed using available evidence (Murad et al. 2017; Kristien Hens et al. 2011; Kristien Hens, Lévesque, and Dierickx 2011; Kyle Bertram Brothers 2011; K Hens and Dierickx 2010).

5.3 Stakeholder involvement

Of 13 broad Reason Mentions supporting increased engagement with patients and their families, 4 discussed the need to clarify misconceptions regarding how their children's genomic data will be used(Goldenberg et al. 2009; A L McGuire et al. 2011; Beale et al. 2015b; Joseph et al. 2008), 1 Reason Mention argued further engagement was needed to confirm patients' rights to access their medical records which may contain genomic data, and 3 Reason Mentions made claims that engagement leads to more informed ethical-legal guidance for data sharing when it reflects public values and priorities. Incentivizing data sharing via appropriate attribution for collecting, storing and analyzing raw genomic datasets is a powerful motivator that 6 broad Reason Mentions claimed facilitates broader sharing. This was particularly true when proper attribution was embedded into national genomics initiatives(A. Holland et al. 2009; M A Majumder et al. 2017).

Indeed, the Universal Declaration of Human Rights codifies the right of scientists to be recognized for their contributions under Article 27(General Assembly of the United Nations 1948)—of which collecting and analyzing raw genomic data may be considered such a contribution. But as one record argues, "the pursuit of scientific truth should prevail over personal or political interests"(Anderson and Merry 2009). In addition to proper attribution, informing data contributors about the ways in which their data will be released—and governance structures are in place to ensure responsible release—play central roles in enhancing patient willingness to share and public trust in data sharers and institutions (10 broad Reason Mentions). Direct stakeholder involvement either as part the shared decision making process, or as participants in future public perceptions research were among the leading methods for enhancing this trust according to 7 narrow Reason Mentions we reviewed.

6. Spectrum and Incidence of Conclusions

We assessed conclusions for all records that were not policies/regulations/laws on the basis of whether the record: 1) proposed a call to action—wherein the authors recommended specific data handling, storage and/or data protection techniques, approaches or protocols to achieve responsible 4R; 2) defined ELSI criteria or assigned 4R responsibility to an appropriate oversight body; included a 3) general discussion of 4R themes related to children without conclusive practical or theoretical suggestions or was a 4) combination of 1 and 2. The ternary plot featured in Figure 2 represents the distribution of publications for which an overall conclusion was drawn (142, 94%), the publications' content type and the context in which data sharing was primarily discussed. We found that 45 (31%) of these publications represented a call to action, 64 (45%) defined ELSI criteria or assigned ethical-legal oversight responsibilities for sharing pediatric data, 25 (18%) included only a general discussion of ethical-legal themes with no prescriptive recommendations, and 8 (6%) reflected both a call to action and defined ELSI criteria.

Figure 2. Ternary plot of 151 documents included in the systematic review by i) content type, the ii) data sharing conclusion drawn and the iii) context in which data sharing was primarily discussed.

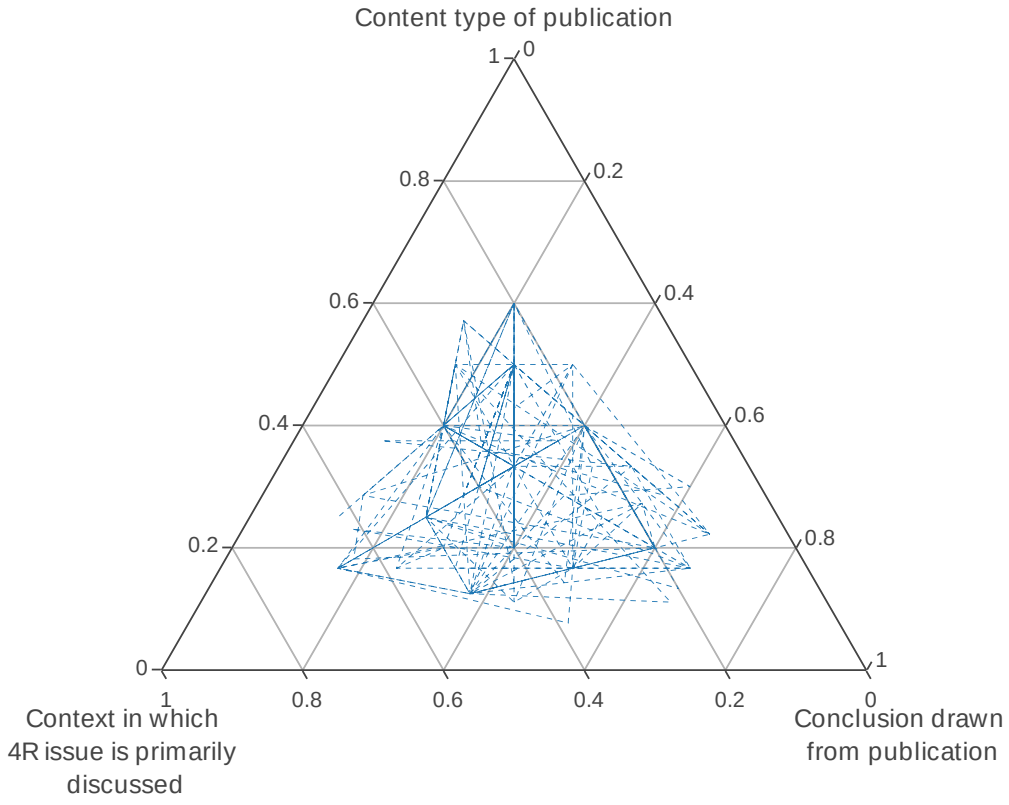


Figure 2 Legend

Code #	Content type	Conclusion drawn	Data sharing context
1	Empirical study	**Call to Action**—Proposes specific data handling, storage and/or data protection techniques, approaches or protocols to achieve responsible 4R, for example ensuring compliant data protections, appropriate de-identification schema, open access publication, explicit consent documents etc.	Biobanking and data repositories
2	Commentary or opinion piece	**Defining ELSI criteria**—Proposes ethical, legal or social criteria or normative principle(s) that promote responsible pediatric data reuse, recombination, repurpose and/or reanalysis, and/or names appropriate oversight bodies	Genetic/genomic research
3	Data sharing guideline/policy	**General discussion** of 4R issues but no conclusive position	Clinical care/clinical database
4	Data sharing SOP/summary of consortium data sharing activities	1 and 2	Epidemiology and Public Health
5	International convention/ guideline/ declaration		Genetic/whole genome/whole exome testing
6	Professional guideline		Identifiable sociodemographic/economic data
7	Regulation		Environmental health
8			Other
9			Human

Reasons Endorsed and Conclusions Drawn

We generalized over all Types of Reasons invoked in call to action conclusions, ELSI criteria conclusions and a combination of the two, to create an overall list of the most-endorsed conclusions drawn (**Table 3**). The rhetorical analyses of competing arguments used to support these overall conclusions informed a suite of policy points to consider published elsewhere (V Rahimzadeh et al. 2018), and are organized into the following categories: 1) Parent and family involvement, 3)

stakeholder involvement, 4) benefits and risks and 5) data governance. Parent and family involvement describes Types of Reasons authors used to defend the idea that responsible sharing should engage parents and patients to the extent possible in decisions related to data sharing. Conceptual ethical-legal arguments under this theme focused exclusively on issues of consent, including recontact of children at the age of majority, and the scope of parents' authority to make broad data sharing decisions for future unspecified uses. The stakeholder involvement theme includes all Types of Reasons to support the roles and responsibilities of external research and clinical stakeholders in 4R data sharing e.g. researchers, institutions, clinician-scientists, funders. Types of Reasons describing the benefits of sharing various types of data—anonymized, coded or otherwise identifiable data—as well as the perceived informational risks associated with accessing data of different types were categorized under Benefits and Risks. Lastly, Reason mentions that proposed how to operationalize responsible data governance through myriad policies, practices and institutional structures were categorized under the theme data governance.

Table 3. Four overarching themes identified across all Types of Reasons (broad and narrow) and the corresponding point to consider proposed for sharing children's genomic and associated clinical data.

Theme	Broad Reason #	Corresponding point to consider (Rahimzadeh et al 2018)
Benefits and Risks	1-10, 15	• All health care professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent. • The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits.
Patient and Family Involvement	11	• The best interests of children are primary. • Children should be listened to and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways. • Parents should be informed in a transparent manner how information regarding their child will be securely managed and used. In a research context, data sharing infrastructures should enable children to withdraw consent when possible on reaching the age of majority. • Parental authorization for ongoing or future unspecified research should include the provision of information related to existing data governance. • Values conveyed by family, legal guardians, or primary caregivers should be respected when possible.

Stakeholder Involvement	16-18	• Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.
Data Governance	12-14	• Duplicative collection of research data involving pediatric patients should be avoided. • Anonymized pediatric data should be made available via publicly accessible databases. Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process.

7. Discussion

Our systematic review found 43 Types of Reasons based on considerations of patient/family involvement, stakeholder involvement, benefits and risks, and data governance to support views regarding responsible sharing of pediatric genomic and associated clinical data. We conclude from all Types of Reasons identified that there is weak support for the position that pediatric data should be treated with special i.e. added protections, or at least with any heightened stringency than that which is afforded to similarly linked genomic and associated clinical data involving consenting adults. Rather, the consequential, incidental and uncertain future of pediatric data substantiates special consideration before, during and after data contribution. These special considerations stem from children's consent-related vulnerability at the time of data contribution, the longitudinal risks implicated when their data circulate in both open, and controlled access databases, and the physical reach of where their data may end up. Parents/guardians, institutions, researchers and clinicians share in the responsibility to discuss such considerations in transparent manners based on the extent of their knowledge.

The reasons analyzed in this review, while not exhaustive, reflect contemporary debates of the policies, practices and technical infrastructures that constitute responsible data sharing in pediatrics, and the relevant ethical-legal principles that ground them. Taken together, the list of reasons as well as their corresponding points to consider give policy makers, institutional data managers and pediatric care institutions looking to adopt genomics-enabled learning health systems a useful starting point from which to develop responsible data governance guidelines/policies.

Our finding that the two most-endorsed reasons for why pediatric data should be shared—to maximize the scientific and clinical utility of children's data (29 total Reason Mentions) and to enhance the prospect of direct and indirect benefits—in part corroborates twin ethical and scientific imperatives one of us defend elsewhere (Rahimzadeh 2017). Furthermore, Types of Reasons given

for 'how' pediatric data should be shared lend evidence that ambiguities in the consent process as well as appropriate data protection strategies are leading concerns for both data contributors and users. While many arguments considered that providing broad consent to share their child's data was within the scope of parental authority, the uncertain immediate clinical benefits may make data sharing more akin to what Brothers et al refer to as 'human non subjects' research (K B Brothers 2011)[xi]. This hypothesis holds especially true of circumstances when researchers seek approval for secondary data uses, and when sharing is not directly pursuant to any clinical decisions e.g. diagnosis, treatment.

Our review also found that responsible data governance and release of pediatric data—assessed in this review in terms of data management, access and protection—is not only executed institutionally by authorized personnel such as data stewards and oversight committees, but increasingly by the technology itself. According to the data sharing protocols and programs we analyzed, specifically, encryption technologies, algorithms and other computational tools are in effect carrying out the protections that normative ethics principles and existing laws/regulations mandate. There are obvious advantages for moving towards this approach we call 'computation-mediated governance', albeit with significant sustainability challenges. Automating processes typically prone to human error make the aforementioned technologies, algorithms and tools particularly effective at reducing data mismanagement and thereby misuse. These processes are not immune, however, to more powerful computational innovations to exploit systems vulnerabilities, and ultimately require institutions to constantly update technical infrastructures to prevent unauthorized access. Our review makes evident that both personnel- and computation-mediated governance are needed to meet the ethical-legal obligations for proportionate governance of children's data.

Many records included in our review provide useful case examples, namely in the rare disease context, of how such a system can be operationalized in the pediatric setting using interoperable data platforms (Forrest et al. 2014; Jernigan et al. 2016). The review gives credence to the varied clinical and research scenarios from which (in)direct benefits could be derived from sharing data, expanding the conceptual notion of best interests that are frequently used—and sometimes abused—to justify interventions involving children. Despite the scientific strengths of

[xi] It is worth noting here the different jurisdictional definitions of what constitutes 'research' and/or data derived from research activities between Canada and the United States. Under the Common Rule, a human subject is a living individual about whom a researcher obtains data from a clinical intervention or other interaction, or identifiable information. Cells or tissue removed during the course of routine clinical procedures and are de-identified are exempt, for example, from institutional review.

bridging research and clinical care that learning health systems typify, our review confirms they remain separate regulatory domains when it comes to sharing data derived from either research or clinical settings. Indeed, some work has been done towards laying the ethical-legal groundwork for such a system(Grady and Wendler 2013; Faden et al. 2013) and there is reason to believe that further guidance on implementation is not far.

8. Limitations

Several limitations should be noted when interpreting the results of this systematic review of reasons. First, our interest in the ethical-legal considerations of sharing required inclusion criteria that was broad enough to encompass literatures across medicine, science and philosophy, policies and data sharing protocols. Extracting the reason-based knowledge from these literatures required a greater reliance on qualitative interpretation and analysis than previously reported systematic reviews of reasons. This was especially important because our review questions also do not lend themselves to binary conclusion—that is for or against data sharing. In addition, the records we included discussed sharing genomic or clinical data, exclusively, as well as those that discussed sharing linked genomic and clinical data together. We did not distinguish between these three types of pediatric data sharing environments in this review. The various Types of Reasons we identified therefore reflect each of these different sharing contexts together and may not be generalizable to all data sharing use cases, jurisdictions and pediatric populations.

Second, two independent reviewers (VR and GB) selected records for inclusion based on the criteria outlined, completed the quality appraisal for empirical studies, and agreed on the initial coding schema. Only the lead author was involved in the coding of and reporting on Reason Mentions according to the agreed upon coding schema thereafter. While not uncommon in qualitative reviews, particularly narrative reviews, this singular coding approach may have resulted in different overall Reason Mention numbers.

Many of the records we analyzed included general discussions of 4R considerations, but do not prescribe 4R data sharing practices for every anticipated use case. The most often reported use case for integrated genomic and associated clinical data sharing were in rare pediatric disease, the ethical-legal considerations and patient data inputs of which can differ significantly when compared to other pediatric clinical contexts such as primary care or mental health.

9. Summary and Conclusions

This systematic review of reasons marries empirical research investigating ethical-legal considerations of data sharing involving children, as well as relevant policies/guidelines governing such sharing. The review substantiates 'why' such sharing is critical to advancing pediatric medicine, and 'how' to realize the benefits therein. We found 18 broad and 25 narrow Types of Reasons based on considerations of children's involvement, parental involvement, stakeholder involvement, balancing benefits and risks and data governance. These reasons provide a discursive landscape of the social, scientific, bioethical and legal arguments upon which sharing children's genomic and associated clinical data are premised. Our review found that actualizing (in)direct benefits of data sharing entails governance approaches that accommodate children's consent-related vulnerabilities—such as to encourage children's assent and participation in the decision-making process, and reconsenting them for continued data use once they reach the age of majority—without obstructing the scientific progress that emerging big data endeavors yield. The broad Types of Reasons we identified that support special considerations for sharing pediatric data may also be transferable to other patient-participant populations with similar consent-related vulnerabilities such as incompetent adults.

This review furthered the theory and practice of data sharing in two primary ways. First, broadening sources of evidence espoused in the records we included affords a high-level overview of the pediatric data sharing phenomenon from myriad perspectives including data contributors, mangers and distributers. The review then maps practices of data contribution, management and distribution onto the ethical-legal premises—drawing on principlist logics applied classically in research and clinical ethics—that the data sharing community ascertains as responsible governance. Second, the ability to empirically support policy options is in the spirit of evidence-based policy making we aspire for genomic data sharing involving children, and thus motivated our review. This review gives equal primacy to philosophy/ commentary/opinion pieces as empirical studies. Implicit in our decision to adopt a review of reasons approach is that these varied sources of evidence have intrinsic value to bioethics policy making (Hammersley 2005), including sources that biomedical science policy has historically discredited for lacking empiricism (Chalmers 2003). Responsible—and responsive—policy infrastructures that allow genomics-enabled learning health systems to thrive require the varied sources of evidence including, but not limited to those we synthesized. Here too,

the list of Reasons and corresponding points to consider offer a helpful start to expanding the evidentiary bases for ethics governance and policy and are currently being validated in a subsequent policy Delphi study in the Canadian context (publication forthcoming).

Further research is especially pressing in several areas, namely characterizing the discreet benefits and informational risks to sharing. The latter disproportionately dominate public discourse, and are fueled by several epic data breaches exposed in recent months [128]. Demonstrating the observable benefits of sharing data together with characterizing the realistic informational risks[xii] are needed to paint both a contemporary and comprehensive picture for prospective data contributors, whose input are essential sources of public evidence from which data ethics governance in the learning health system can build.

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[xii] Several research teams have determined the risk of re-identification based on whole genome sequence data deposited in clinical, and commercial genealogical databases, respectively[130,131]. These efforts, however, reflect purposeful data breaches with the aim of exposing systems vulnerabilities.

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Preface to Chapter 3

Chapter 2 considered the normative ethical principles, policies and practices that constitute 'responsible' sharing of genomic and associated clinical data when this data are derived from pediatric patient-participants. The list of reasons was thematically consolidated into a suite of policy positions that together comprised an initial version of the Key Implications of Data Sharing (KIDS) framework. Chapter 3 describes this consultative process. It details each policy position point in turn, as refined by a consensus working group meeting of the Paediatric Task Team of the Global Alliance for Genomics and Health during its 4th Plenary Meeting held in October 2016.

The need to clarify the ethical-legal bases upon which data sharing governance should rest when such data involve children coincide with two movements so far discussed in this thesis: the imperative to share in the 'omics' disciplines, and reforms to ethics review policies that purport to facilitate collaboration such disciplines typify. Despite the research-care nexuses that the 'omics' disciplines have made possible—and sustained thanks to data sharing—the respective ethical-legal traditions circumscribing appropriate oversight of research and clinical care remain separate and distinct. Chapter 2 highlighted this incoherence in answering *what ethical, legal, and social and scientific factors enable responsible genomic and associated data sharing involving children?* by systematically reviewing the reasons-based literature, including empirical studies and policies/guidelines on pediatric data sharing.

This thesis now turns attention to translating the principles, procedures and policies implicated in responsible data sharing proposed in Chapter 1, and corroborated in Chapter 2, to develop an ethical-legal framework for Canada that takes up these themes. Chapter 3 begins with a methodological overview and study design supporting a three-round policy Delphi according to Turoff (1970). The conflicting ethical-legal obligations that sharing pediatric can give rise make the policy Delphi an ideal method to explore where convergence and divergence lie for this policy issue in Canada. Chapter 3 describes 6 phases of the policy Delphi adopted in this study, including the assessment measures used to determine consensus, the conceptual frameworks guiding data analysis, as well as the sampling strategies used.

CHAPTER 3 METHODS

Methodology

This policy Delphi draws on both qualitative and quantitative data to answer **II**) *how do Canadian pediatricians, genomic researchers, ethicists and bioethical scholars prioritize the ethical-legal, social and scientific factors of genomic and associated clinical data sharing involving children in Canada?* Quantitative data were derived from individual Likert ratings—two ratings for each individual policy position statements—and analyzed using descriptive statistics. This quantitative data was triangulated with written, qualitative data the Delphi panelists provided to justify their ratings. Qualitative and quantitative data were concurrently collected and analyzed to inform subsequent Rounds of the policy Delphi. Quantitative Likert ratings were used to determine degrees of consensus and polarity in Rounds 1 and 2. Qualitative description using thematic content analysis according to Sandelowski (2000; 1993) was then used to nuance the strength and direction of this consensus using panelists' ethical-legal discourse. Round 3, more so than Rounds 1 or 2, relied on this discourse analytical approach to construct the typologies of ethical-legal prioritization that grounds research question **II**. Themes emerging from the qualitative data were inductively analyzed and iteratively applied. One of the strengths of the policy Delphi in this regard is its reliance on staying close to the data to build on, confirm or refute conceptual linkages interpreted in successive rounds. All qualitative themes and results from the statistical analyses were discussed with supervisors after each round, and during the design phase of the subsequent round to maintain methodological rigor and trustworthiness.

Conceptual Framework

This thesis uses qualitative approaches, namely systematic review of reasons and Policy Delphi, to forge the missing link between ethics oversight and data governance towards sharing genomic data in the pediatric infrastructure sciences. The two interrelated studies that comprise this thesis make a theoretical commitment to understanding data sharing governance as a constellation of policies applicable for clinical research and care separately. Implicit in this commitment—and reflected in the research questions posed—is that genomic and associated clinical data sharing is subject to plural ethics governances. Simultaneous compliance with more than one governance regime makes pediatric data sharing akin to what Rein and Schon theorize are policies in a 'negotiatory state' of the rational policy design process (Rein and Schon 1996). Policy making under the purview of plural

governances is, "considered a matter of coproduction between multiple, semi-autonomous, yet interdependent actors" (Hart and Kleiboer 1995). Clinicians, researchers and institutional oversight bodies are primary interdependent actors engaged in negotiating and practicing responsible data sharing policy.

Policy-practice incoherence, however, can result when data sharing originates in clinical care, for example, and then must subsequently comply with norms governing clinical research if data are later repurposed for research uses. On this point Rein and Schon assert that discrepant governance processes are symptomatic of value conflicts; their resolution relies in part on policy action framing, and subsequent reframing. Policy controversies result therefore when value conflicts remain unresolved:

> ...in some cases of controversies policy actors will become motivated to reflect on the nature and appropriateness of their own and other actors' frames, precisely because they become aware that other actors respond in surprising and negative ways to their policy claims, and that the policy process as a whole stagnates. This reconsideration of action frames may result in refraining: actors redefine their situations and will start to redesign their policy proposals. Ideally, this will amount to some kind of synthesis between action frames, and consequently to establishing a context in which conventional bargaining and negotiation between proponents of competing, yet isomorphic, policy proposals can resolve the stalemate…."refraining" is more likely to occur when the controversy is situated in an institutional context, where the price of inertia and protracted policy stalemate can be high. In other words, in many real-world controversies, as opposed to most academic ones, continued controversy prevents conclusive action from being taken to deal with urgent social issues and crises.

Responsible data sharing policy in learning health systems, for instance, can be a recipe for policy controversy based on Rein and Schon's definition (Hart and Kleiboer 1995). Exploring the normative bases of value conflicts among Canadian data sharing stakeholders—recognizing that some may be intractable—motivates asking *how do Canadian pediatricians, genomic researchers, ethicists and bioethical scholars prioritize the ethical-legal, social and scientific factors of genomic and associated clinical data sharing involving children in Canada?* Using qualitative approaches that are uniquely suited to *deconstruct* value conflicts, this thesis *constructs* a living ethical-legal framework that reflects points of value reconciliation among data governance stakeholders in Canada. In this regard, the policy Delphi method aligns squarely with the value elucidation and framework-formulation objective of the thesis.

Definitions

The following terms are taken from the Global Alliance for Genomics and Health Data Sharing Lexicon (Global Alliance for Genomics and Health (GA4GH) 2016).

Accountability— The obligation to explain and justify conduct.
Anonymized/anonymous data— The irreversible delinking of identifying information from associated data.
Big data— Large and complex datasets typically combining multiple sources of information and analyzed through novel computational methods.
Biobank— An organized collection of human biological material and associated data which is stored, processed and searchable.
Coding/ Pseudonymisation—The act of replacing an identifier with a code for the purpose of avoiding direct identification of the participant, except by persons holding the key linking the code and identifier.
Confidentiality—The ethical and legal obligation of an individual or organization to safeguard data or information by controlling access as authorized by law or by the data donor.
Consent— Voluntary and informed expression of the will of a person, or if incompetent, his/her legal representative.
Controlled/ Restricted Access— Access to data that is subject to conditions and an approval process.
Data Access Committee— A committee that reviews and authorizes applications for data access and use.
Data Breach— The unauthorized collection, access, use, disclosure or release of data.
Data Donor/contributor— The individual whose data have been collected, held, used and shared.
Data Linkage—The process by which records representing the same entity or individual are linked across multiple data sources.
Data Protections—The set of laws, policies and procedures that aim to minimize intrusion into people's privacy, uphold confidentiality, and penalize undue intrusions and/or breaches.
Data—Observations, narratives or measurements that are assumed as the basis for further analysis, calculation or reasoning.
Data Security— The protection of the confidentiality, availability and integrity of data.
Data Sharing— Extending access to data for the purpose of research or analyses.
Data Steward—An entity responsible for assuring the quality, integrity, and access arrangements of data and metadata in a manner that is consistent with applicable law, institutional policy, and individual permissions.
Data (or Material) Transfer Agreement— A binding legal agreement between the provider and the recipient of data (or materials) that sets forth conditions of transfer, use and disclosure.
Database— Data and information that are managed and stored in a systematic way to enable data analyses.
Dataset— A collection of data which may be a subset in a database.
De-identification—The removal or alteration of any data that identifies an individual or could, foreseeably, identify an individual in the future.
Ethical Guidelines— A framework to guide decision-making based on accepted ethical principles and practice.
Ethics Review Committee— An independent committee for the ethical review of research activities.
Governance— The process of policy making and management that guides and oversees research in a consistent and structured manner.

Harmonization—The process of unifying certain policies, methodologies and approaches in order to achieve interoperability.
Identifiable/personal data—Data that alone or in combination with other data may reasonably be expected to identify an individual.
Information— Data that have already been interpreted, i.e. they have meaning in a specific context.
Medical record/data—A paper or electronic record created in the health care system which contains medical and health-related information about an individual and is used to record and support health care for that individual.
Metadata—Data that describe other data.
Open access—Making data available without restriction.
Opt-in—A consent mechanism where an active choice is made to participate.
Opt-out—A consent mechanism where consent is implied unless an active choice is made not to participate.
Privacy–The right and freedom to control access to information about oneself.
Public engagement— An inclusive act ranging from the active involvement of a population or sub-population in the development, management or governance of a project, to the provision of information and raising awareness of a project.
Reanalysis—Developing new lines of inquiry and techniques for extracting new information from already collected source data (Collman and Matei 2016).
Recombination— Refers to developing new (meta) information from constituent data sets made available to the investigator. Recombining data potentially enables re-identification of individuals from data that contains no specific identifiers or has been intentionally stripped of identifiers (Collman and Matei 2016).
Registered access— A system of authentication and self-declaration prior to providing access to data.
Re-identification— The act of associating specific data or information within a dataset with an individual.
Repurpose— Refers to taking data originally collected for a specific purpose in a specific domain and analyzing them for unrelated purposes in a domain other than their domain of origin. In addition to the questions posed by reusing data, repurposing big data poses questions about the legitimacy of analyzing data acquired under one privacy context and employing it in a different privacy context (Collman and Matei 2016).
Reuse— Reuse refers to taking data originally collected for a specific scientific purpose and using them again for comparable purposes in comparable domains (Collman and Matei 2016).
Risk— The probability that an event, favorable or adverse, will occur within a defined time interval.
Secondary use— Using data or biospecimens in a way that differs from the original purpose for which they were generated or collected.
Vulnerable Persons /Populations—Individuals or groups requiring special considerations and/or under the protection of governments, institutions or legal representatives including but not limited to children, the elderly, and those with mental health issues.

Scope and Delimitations

This thesis is concerned with the policies, practices and principles of responsible genomic and associated data sharing involving children in Canada. As such, several theoretical and geographical delimitations should be noted. It accepts as a starting point that ethical-legal and social coherence with Canadian laws, policies, regulations and normative documents such as international

conventions together render 'responsible' the governance approaches analyzed herein. Responsible governance has been the focus of rich theoretical and philosophical inquiry to date. Sociologists, bioethicists, science and technology studies scholars and others exemplify the various disciplines that have critically reflected on the ways technology governs, and is governed. This thesis does not, however, engage with the foundational themes and concepts of responsible governance per se, nor the critiques thereof.

The focus on genomic and associated clinical data is also an important delimitation. Omitted from this thesis are the myriad forms and functions of other kinds of clinically relevant data collected from and shared about children. The bioethics orientation of this thesis narrows a focus on data related to health and, further, to emerging sources of genetic data that have only recently been used to inform clinical care decisions involving children. Genomic data linkage with associated clinical data in the electronic medical record, for example, typifies these emerging sources. Moreover, this thesis subscribes to the precedent set forth for genomics-enabled learning health systems that delivering the highest standard of care to children relies on iterative processes between scientifically sound clinical research and clinical care (Beachy, Olson, and Berger 2015).

The thesis also refrains from investigating the ethical-legal bases of sharing incidental findings, or results of whole genome/exome sequencing, which were unanticipated at the time of testing but may be clinical actionable. The clinical thresholds for disclosure, as well as the ethical-legal considerations of such disclosure have received considerable empirical and policy attention. The breadth of empirical studies and related guidelines therefore justifies a renewed focus on elective genomic and clinical data sharing that is taken up in this thesis.

Finally, there are geographic delimitations when studying the application of responsible data sharing policies, practices and principles in one national jurisdiction. Canada fulfilled practical and theoretical ideals in this regard. Prior engagement with the pediatric clinical research and professional genomics communities in Canada potentiated favorable participant recruitment in the policy Delphi. Moreover, province- and territory specific adherence to research ethics oversight for data sharing under the Tri Council Policy Statement 2 (TCPS2) and other federal frameworks guiding responsible conduct of research makes Canada a unique jurisdiction in which to study how the clinical care-research distinctions problematize scientific collaboration in genomics.

Research Design and Rationale

The RAND Corporation is credited with devising the first Delphi study, referencing the Oracle of Delphi from which the method derives its name. In the throes of the Cold War, the United States Air Forces Secretary commissioned RAND to advise defense leaders on how to respond to nuclear threats by soliciting expert opinions in a systematic way (Sackman 1974). Delphi studies have since expanded beyond military applications to: forecast sociotechnical futures concerning emerging technologies (Grupp and Lindstone 1999), including those in genetics/genomics (Esmail et al. 2013; Birko, Dove, and Özdemir 2015a; Oberg et al. 2015; Messner et al. 2016); and to critically assess competing ethical, legal and social interests that emerging technologies inevitably raise and that could be used to inform public policy.

The analytical features of early Delphi studies have also broadened to incorporate richer sociological approaches that afford "structure[ed] communication between a group of people who can provide valuable contributions in order to resolve a complex problem"(Landeta 2006, 468). More recent Delphi studies preserve several key attributes of their RAND precursors, namely the process of iterative consultation and controlled feedback among a group of pre-selected knowledge experts with the aim of achieving consensus. Participation on the Delphi panel is typically anonymous and known only to the study coordinator. This discreetness allows for a "working process [to] be developed with experts who do not coincide in time or space and also aims to avoid the negative influence that could be exercised by factors in the individual answers in terms of the personality and status of the participating experts"(Landeta 2006, 469). Keeney et al identified ten Delphi modalities that vary in their semblance and application to the classical Delphi. "The Delphi design adopted," as Hasson et al rightly argue, "is situational in that it is guided by the research problem rather than by the requirements of a method. Some are specific techniques whilst others incorporate either wholly or partly some designs"(Hasson and Keeney 2011).

Responsible sharing of genomic and associated data constitutes a policy question in a negotiatory state. That is, negotiations related to the politics, problems and processes of data sharing involving children are contemporaneous and ongoing across actor networks e.g. researchers, clinicians, institutions and governments (Hart and Kleiboer 1995). That such policy negotiations are not, for example, imagined sociotechnical futures for which forecasting methods associated with classic Delphi studies are more commonly applied, supports adopting a modified Delphi method

that better coheres with the negotiatory state of this policy issue. Schmidt too critiques the future framing of conventional Delphi studies, arguing

> The future can be conceived of as a hypothetical dynamic system subject to the influence of past events, random occurrences, and purpose-creating systems. This is in contrast to a static view of the future, such as divine preordination, where the forecaster's role is to search for ways of unveiling future events that have already been determined. Social events are subject to the influence of policy, and policies often represent the governing forces that produce social events. Individual forecasts made by different persons are bound to be based on diverse policy assumptions. Rather than being interested in a specific event as the outcome of unspecified policies, decision-makers are often more interested in the policies that would produce the event, or in an exploration of the relationship between specified policies and various events. Delphi studies that do not explore the assumptions underlying a forecast are, therefore, of limited utility to decision-makers.

The policy Delphi proposed by Lindstone and Turoff is conducive to studying the contemporal and negotiatory logics of policy development first articulated by Hart and Kleiboer (1995), and was chosen explicitly for these reasons to guide this thesis. The policy Delphi is a structured communication process that systematically solicits informed judgments on a policy question of interest, and provides controlled feedback on the results of that consultation (M Turoff 1970). Like Baumann et al, the policy Delphi adopted herein "is generally less oriented toward long-range future, seeks informed panelists as opposed to experts, is concerned with identifying conflict as well as with the formation of consensus and places primary emphasis on the discovery and articulation of policy alternatives and options" (Baumann, Ervin, and Reynolds 1982, 722).

The goal is to nuance perceptions, values and priorities implicit in policy agendas, and to provide a platform for idea exchanges on policy alternatives in light of these perspectives (Meskell et al. 2013). Turoff, a pioneer in the practical application and theoretical substantiation of the policy Delphi considers it a forum for ideas to address policy questions involving "vital aspects, such as goal formation, for which there are no overall experts, only advocates and referees. Its resolution must take into consideration the conflicting goals and values espoused by various interest groups as well as the facts and staff analyses" (Lindstone and Turoff 2002, 71). In this way, the Policy Delphi serves as a "precursor to committee activities" that "revive the advocacy process in government through improving the effectiveness of lateral policy formulating committees" (Turoff 1970, 153) towards the resolution of a proposed policy question.

Also in contrast to the conventional Delphi, the "policy Delphi is thought of as a decision-facilitation tool"(de Loe 1995, 57). Cookson (1986) helps to further illustrate the conceptual and analytical differences between conventional and policy Delphi models:

> As distinct from Delphi, Policy Delphi does not seek to establish consensus relative to a specific reality. Rather it makes allowance for and indeed encourages elucidation of not only convergent but also legitimate and valid divergent responses. It is particularly useful when the focus is not on consensus per se, but rather on exploration of alternatives, and pro and contra arguments for those alternatives (Cookson 1986, 5).

The conflicting ethical-legal obligations relevant for data sharing in genomics-enabled learning health systems, as well as the special data protection considerations when genomic data involve children underpin why the policy Delphi is an ideal method to explore where convergence and divergence lie on this policy question in Canada. The strength of the policy Delphi as a decision facilitation/analysis tool moreover aligns with framework-formulation objective this thesis aims to meet. While sharing procedural elements with classic Delphi studies, the following structure guided the policy Delphi study designed to answer research question **II** of this thesis:

> 1. **Formulation of the policy issue**—What is the issue that should be under consideration? How should it be stated?
> 2. **Exposing the options**—Given the issue, what are the policy options available?
> 3. **Determining initial positions on the issues**—Which are the ones everybody already agrees upon and which are the unimportant ones to be discarded? Which are the ones exhibiting disagreements among respondents?
> 4. **Exploring and obtaining the reasons for disagreements**—What underlying assumptions, views or facts are being used by the individuals to support their respective positions?
> 5. **Evaluating the underlying reasons**—How does the group view the separate arguments used to defend various positions and how do they compare with one another on a relative issue?
> 6. **Re-evaluating the options**—Re-evaluation is based upon the views of the underlying 'evidence' and the assessment of its relevance to each position taken (Lindstone and Turoff 2002, 84)

The systematic review of reasons reported in Chapter 2 was combined with a key informant committee meeting to accomplish **Phases 1-2** in the Policy Delphi process: formulate the policy issue and exposing the options. The review of reasons that drew from the pediatric genomic data sharing literature—including relevant policies, guidelines and regulations—considered whether, and how genomic data involving children should be shared. Members from the Paediatric Task Team of the Global Alliance for Genomics and Health met during the 4th Plenary Meeting in October 2016 to determine initial positions on the ethical, legal, social (ELSI) and scientific issues related to pediatric data sharing identified in the review of reasons **(Phase 3)**.

The key informant meeting resulted in a refined list of ten policy positions to consider for

sharing genomic and associated clinical data involving children. These positions comprised the Key Implications of Data Sharing (KIDS) framework that served as the basis for a 3-round policy Delphi study among Canadian pediatric data sharing stakeholders.

It is worth reminding the systematic review and key informant group that together informed the KIDS framework were both internationally focused. The federated healthcare funding and research system in Canada, however, warrants investigation into the jurisdiction-specific translation of the policy positions proposed in the KIDS framework. The policy Delphi was completed entirely online so as to achieve geographic representation and enhance feasibility. The design and rationale for each of three Delphi rounds are described separately below[xiv].

Round 1

The first round of the policy Delphi assessed 12 policy positions; two of the initial 10 policy statements were divided to facilitate rating. Respondents rated the 12 policy positions using a 4-point Likert scale[xv] on the basis of 2 of 4 measures outlined in the methods literature (Lindstone and Turoff 2002): relative importance, desirability, confidence and feasibility (**Table 4**). The 2 ratings were selected for each of the 12 statements based in combination of findings from the systematic review and consensus meeting discussions[xvi]. Turoff suggests limiting ratings to no more than two. This minimizes rater fatigue, one of the primary reasons for participant attrition[xvii]. Respondents were required to provide written justification for each policy position they rated. They were also given the option to revise any existing policy position or suggest new positions that would undergo

[xiv] Delphi surveys were not predetermined, but rather designed iteratively based on data analysis following successive rounds (see **Data analysis plan**).

[xv] Here again, the outcomes of interest and primary data collection in this policy Delphi were positions, arguments, and decisions regarding a proposed ethical-legal framework for data sharing involving children. The policy positions comprising the framework, while supported in the literature and a key informant committee were "designed to elicit conflict and disagreement, as well as to clarify opinions" (Meskell et al. 2013, 33). Neutral responses were therefore not permitted, supporting adoption of the 4-point scale.

[xvi] For example, 3 broad Types of Reasons identified in the review of reasons confirmed the view that maximizing the child's best interests either directly or indirectly was a desirable outcome of sharing their genomic and associated clinical data. Members of the consensus working group likewise corroborated the desirability of fulfilling best interests, yet debated whether the merits of sharing children's data rests entirely on their ability to deliver on these interests, citing concerns about feasibility. Relative importance and feasibility were therefore selected as the two rating items for policy statement 1: *The best interests of children are primary*.

[xvii] The strict time constraints of the respondent population of interest, practicing clinician-scientists in this case, accentuated the need to design survey rounds that could feasibly and consistently be completed around clinic schedules.

review during Round 2. Examples of concise, specific forms of qualitative feedback were provided to panelists to encourage them to mirror this style of response when completing the survey. The qualitative data accompanying each numerical rating was then coded using thematic content analysis (Sandelowski 2000).

Individual policy positions were adopted for inclusion in the KIDS framework if and only if they achieved 1) high consensus, 2) low polarity and 3) strong- to weak support based on numerical ratings; and if panelists invoked similar ethical-legal rationales corroborating consensus on the policy statement based on a synthesis of the thematic codes created from the qualitative data. Statistical thresholds for consensus, polarity and support served merely as proxy indicators, rather than determinations of consensus and dissent on policy positions. That is, only policy positions that indicated low consensus, high polarity and strong opposition according to numerical thresholds as well as qualitative rationales were preserved for re-assessment in subsequent rounds.

Table 4. 4-point Likert scale for relative importance, desirability, confidence and feasibility (adopted from Turoff 2002).

	1	**2**	**3**	**4**
Desirability (Effectiveness or Benefits)	**Very Desirable**	**Somewhat Desirable**	**Somewhat Undesirable**	**Very Undesirable**
	• Will have a positive effect and little or no negative effect • Extremely beneficial • Justifiable on its own merit	• Will have a positive effect and little or no negative effect • Beneficial • Justifiable as a by-product or in conjunction with other items	• Will have a negative effect • Harmful • May be as a by-product of a very desirable item, not justified as a by-product of a desirable item	• Will have a major negative effect • Extremely harmful • Not justifiable
Feasibility (Practicality)	**Definitely Feasible**	**Possibly Feasible**	**Possibly not Feasible**	**Definitely not Feasible**
	• No hindrance to implementation • No research and development	• Some indication this is implementable • Some research	• Some indication this is unworkable • Significant unanswered questions regarding	• All indications are negative • Unworkable • Cannot be implemente

	required • No political roadblocks • Acceptable to the public	and development required • Further consideration or preparation to be given to public reaction	implementation	d
Relative Importance (Priority or Relevance)	**Very Important**	**Somewhat Important**	**Somewhat Unimportant**	**Very Unimportant**
	• A most relevant point • First-order priority • Has direct bearing on major issues • Must be resolved, dealt with or treated	• Is relevant to the issue • Second-order priority • Significant impact but not until other items are treated • Does not have to be fully resolved	• Insignificantly relevant • Third-order priority • Has little importance • Not a determining factor to major issue	• No relevance • No priority • No measurable effect • Should be dropped as an item to consider
Confidence (Validity of the Argument or Premise)	**Certain**	**Reliable**	**Risky**	**Unreliable**
	• Low risk of being wrong • Decisions based upon this will not be wrong because it represents 'fact' • Most inferences drawn from this will be true	• Some risk of being wrong • Willing to make a decision based on this but recognizing some chance of error • Some incorrect inferences can be drawn	• Substantial risk of being wrong • Not willing to make a decision based on this • Many incorrect inferences can be drawn	• Great risk of being wrong • Of no use as a basis for decision

Round 2

Panelists were shown their original ratings as well as a summary of all Round 1 results, including

qualitative feedback. They then re-rated those policy positions that, according to both the numerical ratings and qualitative analysis, indicated low consensus and weak- to strong polarization. Any amendments to existing policy positions or new positions suggested after Round 1 were also included for assessment during Round 2. Panelists' original ratings, the group average and all qualitative responses were visible for each policy position under review in Round 2. Panelists were instructed that they could change or preserve their original rating. Policy positions, amendments and additions that did not meet the numerical thresholds for consensus as corroborated by their qualitative rationales were subsequently kept for further analysis in Round 3.

Round 3

Panelits were provided summary results, including qualitative rationales collected during Round 2. Round 3 targeted attention on the policy positions that after 2 ratings and amendments continued to elicit highly polarizing opinion and low consensus. Round 3 sought to identify and qualify the ethical-legal tensions underpinning this polarity. The end products of the policy Delphi after Round 3 were twofold: a suite of policy positions that reflected convergence on ELSI priorities for sharing genomic and associated clinical data sharing involving children according to Canadian stakeholders and, importantly, why they consider them priorities (de Loe 1995). Second, rich qualitative data nuancing the specific ethical-legal and social divergence on policy positions in the Canadian pediatric genomics context.

Population

In order to maximize the transferability of the results and ensure statistical feasibility (Birko, Dove, and Özdemir 2015b), Lindstone and Turoff propose at minimum 10, and a maximum of 50 informed 'advocates' and 'referees' to serve as panelists in the Policy Delphi. Consistent also with the design rationality framework guiding this thesis, Lindstone and Turoff take a critical stance on 'expertise' given the multidisciplinary nature of policy questions and policy-making processes. Informed 'advocates' or 'referees' were eligible if they met one of the following characteristics: they were a practicing clinician who shares genomic and associated clinical data involving children as a regular feature of their clinical practice; they were a pediatric genomic researcher who generates, manages and shares genomic and associated clinical data; they served as a member or chair of a pediatric research ethics board that reviews scientific protocols involving genomic and associated clinical data sharing involving children; or their research centered on ELSI themes related to sharing genomic and associated clinical data involving children.

Sampling and Sampling Procedures

A purposive sampling strategy was used to identify prospective Delphi panelists who met the above inclusion criteria. Lead clinician-investigators from Genome Canada's large-scale, genomics and personalized health (GAPH) projects were recruited, as well as ethicists involved in reviewing these projects across Canada. Genome Canada launched the first Large-Scale Applied Research Project Competition centered on personalized medicine in May of 2010, and a second competition in 2012. Both competitions funded pan-Canadian projects that uncovered "how genomics-based research can contribute to a more evidence-based approach to health and improving the cost-effectiveness of the health-care system" (Canada 2015). Lead investigators and pediatric ethicists from the GAPH program if:

- The project as pediatric-specific with a focus on diseases affecting children or adolescents (newborns to age 18)
- The project was multi-site and/or multi-jurisdictional
- The project obtained approval, or is in the process of obtaining approval from the appropriate REC(s)
- The project involved the collection, use and analysis of sequence data and/or biological samples from children

Seventeen GAPH projects were funded across both competitions, 6 of which involved pediatric patients or focused on elucidating genomic etiologies of pediatric diseases (**Table 5).**

Table 5. Pediatric-specific projects funded as part of Genome Canada's Large-Scale Applied Research Project Competition (2010) and the Genomics and Personalized Health Competition (2012)

Year funded	Project details
2010	**Stratifying and targeting pediatric medulloblastoma through genomics** PIs: Michael Taylor, Marco Marra, David Malkin Hospital for Sick Children
2012	**Personalized medicine in the treatment of epilepsy** PI: Patrick Cossette Centre hospitalier universitaires de l' Universite□ de Montre□ al
	Biomarkers for pediatric glioblastoma through genomics and epigenomics PI: Nada Jabado McGill University Health Centre

	Enhanced CARE for RARE genetic diseases in Canada PI: Kym Boycott Children's Hospital of Eastern Ontario and University of Ottawa
	Autism spectrum disorders: Genomes to outcomes PI: Stephen Scherer The Hospital for Sick Children
	The microbiota at the intestinal mucosa-immune interface: A gateway for personalized health PI: Alain Stintzi Children's Hospital of Eastern Ontario and University of Ottawa

Procedures for Recruitment, Participation, and Data Collection

Lead investigators of the 6 pediatric-specific GAPH projects, as well as the chairs of the research ethics boards at each of the respective institutions named in the funded project were invited to participate via electronic mail (43 individuals total). Contact information (either email or office telephone) was publicly available for all invited participants. All 43 individuals received an email invitation using LimeSurvey. The email invitation included a unique token, described the purpose of the study, the benefits and risks of participating in the Delphi study, as well as provided all study-related contact information for the lead investigators. Interested panelists used their unique token to access all Delphi surveys. Demographic information was collected once before completing the first round of surveys, Round 1 for most panelists. Panelists indicated their consent to participate before each survey. They were free to withdraw from the study at any time by exiting out of the survey and requesting via email that their data be withdrawn, if desired.

All data were collected electronically using LimeSurvey and exported into Microsoft Excel for secure storage and analysis. Because of the iterative nature of the Delphi study, survey data was simultaneously collected and analyzed at 3 discreet points—after each of the 3 Rounds—and participants were effectively debriefed on the results of the prior round of surveys each time they accessed a new survey. Three members of the study team were involved in survey design (VR, GB, BMK). Policy Delphi method experts Murray Turoff (Murray Turoff, n.d.) and Robert de Loe (de Loe, n.d.) were consulted on all elements of the policy Delphi design and data analysis plan presented hereafter.

Pilot Study

Three or more individuals piloted each survey for comprehension, format and clarity prior to data collection. The pilot facilitated in identifying policy positions or rating schema that were unclear or confusing to readers. In addition to the survey design team (VR, GB and BMK), individuals unfamiliar with the main study, those with expertise in survey design and familiar with the policy area, as well as those who were ineligible to participate were contacted to pilot each the Delphi surveys prior to their official launch.

Data Analysis Plan

As other policy Delphi scholars confirm, the group's assessment is the essence of the policy Delphi (Manley 2013), which this thesis captured using both descriptive statistics and qualitative approaches. A classification system according to consensus rankings and support was chosen to meet the following thesis objectives: To assess the relative importance, feasibility, desirability and confidence of policy positions outlined in the KIDS framework; To identify areas of consensus and dissension on the proposed KIDS framework among Canadian stakeholders involved in pediatric genomic data sharing. A consensus rankings and support system—as opposed to the interquartile range used on most conventional Delphi studies— was adopted. This system uses descriptive statistics as a benchmark, together with qualitative responses to shed light on "whether the group supported, opposed, or was ambivalent towards an option; whether the group was split…or whether no clear picture of support emerged" (de Loe 1995, 61) with respect to the policy positions comprising the KIDS framework. Capturing the discursive elements of consensus and polarity with the consensus ranking and support approach to data analysis more closely aligns with the decision-facilitation spirit of the policy Delphi (Lindstone and Turoff 2002). It facilitates decisions by identifying where convergence and divergence lie from both a rhetorical and statistical account. Statistical thresholds alone can be arbitrary in this regard, and misrepresent—or worse ignore entirely—the ethical-legal, social and scientific reasons for consensus and dissent (de Loe 1995).

All descriptive statistics and qualitative text data were analyzed in Microsoft Excel. The consensus and support system applied a consistent set of rules for analyzing ratings. The median and IQR was used to summarize the degree of support and spread in the distribution, respectively, to screen those policy positions that should be retained for re-assessment in subsequent rounds. The statistical parameters for consensus (**Table 6**), polarity (**Table 7**), and support (**Table 8**) were adopted from de de Loe (1995), which were among the only published parameters in the methods literature for policy Delphi studies at the time of analysis.

Table 6. Parameters for consensus: measures the degree to which the group was able to agree on support.

	Parameter
High	70% of ratings in 1 category, or 80% in 2 contiguous categories
Med	60% of ratings in 1 category, or 70% in 2 contiguous categories
Low	50% of ratings in 1 category, or 60% in 2 contiguous categories

Table 7. Parameters for polarity: measures whether the group's ratings were polarized (e.g. 10 0 0 10 is a strongly polarized distribution). Categories include strong, weak, none. Polarity is determined using the variance (VAR.S) of the distribution.

	De Loe 1995	**Rahimzadeh 2018**[xviii]
Strong	Higher than 1.5	Higher than 1.1
Weak	Between 1.2 and 1.5	Between 0.8976 and 1.1
None	Less than 1.2	Less than 0.8976

Table 8. Parameters for support: indicates where the group's support lay when there was *consensus*. When consensus is 'none', support is always 'ambiguous'. It can also be 'ambiguous' when:
(1) the level of consensus is 'low' and the ratings are divided equally between two categories (e.g. rating distributions of 10 0 0 10, or 10 0 10 0);
(2) the ratings are distributed in a pattern such as: 4 10 4 2. In this case, consensus would be considered 'medium'-but the point of support could be either of 'SS-WS' or 'WS-WO'.

	Support code
Strong Support	SS
Strong, to weak support	SS-ws
Weak support	ws
Weak support, to weak opposition	ws-wo
Weak opposition	wo
Weak, to strong opposition	wo-SO
Strong opposition	SO

Policy Delphi Limitations

While lauded for its contributions to empirical policy research, Delphi studies have also been the focus of methodological critique. The rigor involved in selecting the Delphi panel, interpreting consensus/dissension, and panel attrition posed the greatest threats to validity of findings emerging from this policy Delphi. First, the panel was comprised of informed stakeholders representing the

[xviii] Thresholds for polarity were transformed to the 80th percentile based on highest variance of the distribution calculated in the Round 1 dataset (1.122), modification approved after consultation with de Loe(de Loe, n.d.)

practitioner, policy and research perspectives on genomic data sharing involving children. The panelists therefore varied in their data sharing experience and exposure. Recruiting panelists based on these criteria abandons the notion that there are singular policy experts on pediatric data sharing, emphasizing instead panelists' roles as advocates and referees (Lindstone and Turoff 2002) with disciplinary experience needed to understand where consensus/dissension lies in contemporary data sharing theory and practice. Consensus was interpreted by triangulating statistical as well as thematic codes to enhance trustworthiness.

Second, policy Delphi studies typically solicit open-ended feedback during Round 1 to frame the policy issue of interest (**Phase 1**) and determine initial positions on this issue (**Phase 2**). A systematic review as well as key informant committee meeting pre-formulated the issue and determined initial positions on the ethical-legal, social and scientific considerations of data sharing in this policy Delphi study. While not the first policy Delphi to preformulate the policy issue in this way (Meskell et al. 2013; Poba-Nzaou et al. 2016), it is possible that the Canadian panelists who participated in **Phases 3-6** may have formulated the issues differently than the key informant committee. Panelists could have also arrived at different initial positions than those used for initial assessment in Round 1 of the policy Delphi. That several Canadian panelists participated in both the key informant consensus meeting as well as the policy Delphi exercise helped ensure the framework's contextual relevance. Their dual participation was advantageous in two ways: first, to reduce external threats to validity that could have resulted when moving from an international, to a jurisdiction-specific translation exercise; and second to be able to represent through qualitative feedback the spirit and thought-processes that guided the initial key informant group.

It is worth reminding the policy Delphi was adopted to measure the nature and strength of dissension and consensus on individual policy positions that comprise the KIDS framework from the perspective of Canadian data sharers involved in pediatric genomics. This objective has implications for interpreting consensus as well as in planning for effective knowledge translation of the KIDS framework. Each policy position was rated relative to 2 of 4 predetermined considerations e.g. relative importance, desirability, feasibility and/or confidence. The aforementioned considerations are not exhaustive, to be sure. Albeit not evaluated in this policy Delphi, myriad other considerations are likewise relevant for policy framing, formation and implementation. Also, these measures were customized for each policy position based on findings from the systematic review and which the key informant meeting reified. The resulting KIDS framework, in turn, reflects individual policy positions where consensus, support and polarity have been validated across two, non-identical ratings.

Turoff (1970) confirms it is a common danger for panelists to misinterpret the policy Delphi as a decision-making too, and rather emphasizes the method's utility as a decision analysis tool. This danger is relevant to managing knowledge translation expectations, namely that consensus is not a guaranteed outcome of the policy Delphi. Indeed, "it is consistent with the objective of a Policy Delphi to choose a respondent group such that a consensus is unlikely to occur" (M Turoff 1970, 96). The decision-facilitation objective of the study was clarified in all internal communications with panelists—including invitations, the informed consent form and in writing prior to completing each new survey. A list of pediatric data sharing positions supported from a systematic review of the literature as well as findings from a key informant committee were provided.

Delphi processes that rely heavily on qualitative interpretation can also risk manufacturing artificial consensus. This can occur when inappropriately taking panelists' responses out of context and re-organizing results during the controlled feedback in ways imply consensus or dissension when neither may in reality be the case. These examples are threats to internal validity that can lead to methodological misuse. This policy Delphi adopted two workable approaches to the above threats to trustworthiness.

None of the qualitative responses were altered when delivering controlled feedback to preserve the rhetorical and stylistic features of panelist responses. In addition, VR member-checked with panelists prior to modifying any controlled feedback if modifications were required for clarity to ensure the modified response conveyed the respondent's original intent. Moreover, statistical parameters for consensus, polarity and support were not pre-approved by policy Delphi respondents as some researchers suggest helps maximize construct validity. Interpretations emerging from these constructs across Rounds 1 and 2 were fed back to Delphi panelists for internal checks (Schmidt 1997; Okoli and Pawlowski 2004). This approach "can permit validation. Doing this ensures the experts' definitions are correct and increase the likelihood that the findings can be generalisable to different settings" (Hasson and Keeney 2011, 1700) as Hasson et al recommend.

Ethics Review Approval

This study was granted all requisite ethics approvals and continuing review renewals by the McGill University Institutional Review Board (IRB). Because participant recruitment followed a purposive sampling strategy, only email invitations were considered promotional materials and approved accordingly by the IRB. Individuals who met the selection criteria were invited to participate in the study via electronic mail and using a unique digital token. The token served as the only identity-preserving link connecting the panelist to their data. Only the study lead (VR) had access to study

participant keys, which were secured behind a password protected laptop and user account in LimeSurvey. Prior to accessing any of the online Delphi surveys, participants were directed to a landing page where an informed consent document detailed the purpose of the study; the research procedures specific to the corresponding Delphi Round in which panelists were about to take part; the anticipated risks/benefits of their participation in the Delphi study; as well as all identifying study information including contact details for study team; information on the study funder and contact information for the McGill IRB Ombudsperson were also provided in accordance with institutional as well as national research ethics guidelines. The letter of invitation also indicated the types of professional background and expertise reflected in the participant group to confirm respondents were indeed participating in a peer group exercise.

Individuals indicated their official consent by clicking 'next' on the landing page and were directed to begin the survey. All ethics approval certificates, email invitations as well as informed consent documents submitted to the McGill IRB are provided in **Appendix C**. The research activities proposed in this thesis posed minimal risks to participants according to Canadian (Canadian Institutes of Health Research Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada. 2014) and international guidelines (World Medical Association 2013). Risks to participants involved in the policy Delphi component of this thesis were chiefly informational, and specific ethical considerations related primarily to the nature and selection of stakeholder 'expertise' and handling Delphi survey data.

Representativeness and justice

Theoretical representativeness ensures that interested members of the pediatric data sharing and research ethics community are afforded the opportunity to improve the policy aspects of their work, and that the benefits and burdens of the proposed research are distributed proportionately across this population. Recruiting among populations with particular stakes in the policy issue of interest—data sharing in pediatric infrastructure science—is not only critical to the success of the Policy Delphi, but also fulfills principles of social and distributive justice (Canadian Institutes of Health Research Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada. 2014). That the policy Delphi emphasizes recruitment of 'advocates' and 'referees' speaks directly to this point. It also informed the decision to recruit participants involved in the 6 pediatric-specific Genome Canada projects and their respective ethics review oversight committees.

Research data handling

Like the ELSI components of data protection considered in this thesis, the protection of data generated and analyzed throughout the research process was an ongoing ethical exercise. Delphi survey data, including individual ratings and linked qualitative responses were coded. All survey data were secured behind password-protected devices and access was limited only to the primary researcher (VR) and co-supervisors (GB +BMK) where required during thesis committee meetings and review of earlier drafts of this thesis.

In contrast to in-person focus groups—where anonymity and confidentiality cannot be guaranteed—the Policy Delphi was conducted entirely online. The absence of such group interaction is an advantage from both feasibility and data protections standpoints. The anonymity the online Delphi process afforded also lessened the potential for asymmetric power dynamics and group think, the latter of which can place undue pressure on panelists to support the views of panelists more senior to them.

In addition to negatively affecting participant experiences, such pressure could threaten scientific integrity. Delphi studies rely on collegial exchange and deliberation to reflect where true convergence and divergence lie on policy questions of interest. Preserving participant anonymity prevents over-representing dominant voices and neutralizes the power that such stated opinions could reinforce when made known to respondents in Rounds 2 and 3. No participant requested to withdraw their participation or any collected data from the study, and no complaints were filed with the McGill IRB at the time of writing.

Preface to Chapter 4 [Manuscript 3 published in *JAMA Pediatrics, 2018*]

In landscaping the ethical principles, policies and practices that constitute 'responsible' sharing of genomic and associated clinical data, Chapter 2 achieved Phase 1 of the policy Delphi study: formulation of the policy issue. A comprehensive list of reasons supporting 'why' and 'how' genomic data should be shared were thematically consolidated into a suite of policy positions comprising a draft framework. A key informant meeting was then organized to expose data sharing stakeholders to the proposed policy issues and options identified in the systematic review in Phase 2 of the policy Delphi. Members from the Paediatric Task Team of the Global Alliance for Genomics and Health met during the 4th Plenary Meeting in October 2016 were convened to achieve Phase 2. Chapter 4 describes this consultative process and presents the Key Implications of Data Sharing (KIDS) framework for pediatric genomics that resulted from this key informant meeting.

This manuscript was published in the *Journal of the American Medical Association Pediatrics* in 2018 and appears in this thesis with full copyright permissions from the Journal. All co-authors are members of the key informant committee who participated in refining the original KIDS framework i.e. Phase 3 of the policy Delphi study. V. Rahimzadeh led in the organization of the key informant meeting during the 4th Plenary of the Global Alliance for Genomics and Health in Vancouver, British Columbia (Canada); all data collection during the meeting; analysis of meeting results and consensus points; all coordination of committee feedback on earlier drafts of the KIDS framework and preparation of all versions of the manuscript, including the final version with approval from the committee. Funding from the following sources supported publication of this manuscript: Vanier Canada Graduate Scholarship (CIHR#358258); Canada Research Chair in Law and Medicine; and Precision Medicine Policy Network. The results of the key informant committee process as well as the KIDS framework were presented at 3 international conferences in 2017, including the UNESCO Chair in Bioethics; North American Primary Care Research Group Annual Meeting, and at the American Association for the Advancement of Science.

It is important to note the systematic review and key informant meeting that together informed the initial KIDS framework were both internationally focused. The federated healthcare funding and research system in Canada, however, warranted investigation into the jurisdiction-specific translation of the policy positions proposed in the KIDS framework, motivating the policy Delphi study described in Chapter 3. The initial positions described in Chapter 4 then served as the basis for a three-round policy Delphi to assess the framework's application in the Canadian pediatric data sharing context, specifically. These results are presented in Chapter 5.

JAMAPediatrics | SpecialCommunication

Key Implications of Data Sharing in Pediatric Genomics

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JAMA Pediatr. 2018;172(5):476-481. doi:10.1001/jamapediatrics.2017.5500 Published online March 19, 2018.

Abstract

Accurate clinical interpretation of children's whole-genome and whole-exome sequences relies on comparing the patient's linked genomic and phenotypic data with variant reference databases of both healthy and affected patients. The robustness of such comparisons, in turn, is made possible by sharing pediatric genomic and associated clinical data. Despite this, sparse ethical-legal policy attention has been paid to making such sharing routine in practice. The interdisciplinary Paediatric Task Team of the Global Alliance for Genomics and Health considered in detail the current ethical, legal, and social implications of sharing genomic and associated clinical data involving children. An initial set of points to consider was presented at a meeting of the Paediatric Task Team at the 4th Plenary of the Global Alliance for Genomics and Health. The Key Implications for Data Sharing (KIDS) framework for pediatric genomics was developed based on feedback from this group and was supplemented by findings from a critical appraisal of the data-sharing literature. The final points to consider that comprise the KIDS framework are categorized into the following 4 primary themes: children's involvement, parental consent, balancing benefits and risks, and data protection and release requirements.

Scientific Rationale for Pediatric Data Sharing

Genomics and the delivery of precision medicine are data- intensive ventures that require collaboration among researchers and clinicians alike.[1] Responsible sharing of genomic and clinical data drives the continuous feedback of discovery research to clinical care and back again.[2] Combining genotypic and phenotypic data yields the most clinically useful evidence toward this end, informs pediatric-specific treatments, and improves understanding of possible genetic and genomic determinants of complex childhood diseases.[3] Clinical diagnoses for children with rare disease variants or those of unknown significance depend on statistically robust associations between variant frequencies and phenotypic comparisons between children with particular diseases and those without. Therefore, sharing pediatric data that are appropriately accessible is especially pressing when patient populations are small and opportunities for genotype-phenotype comparisons are limited.

By *pediatric data sharing* we mean the broad exchange of genome sequencing data and associated clinical descriptors from an individual pediatric patient, either as part of clinical care or research. Pediatric genomic and associated clinical data may include, but are not limited to, specific characterization of genetic variants and their associated clinical phenotypes, all whole-genome and whole-exome variants, and links to detailed genotypic and phenotypic profiles of pediatric patients and their unaffected family members.

Restricted access to data is partly to blame for current barriers to responsible data sharing,[4] including in pediatrics. For jurisdictional reasons, there are clear distinctions between clinical, research, and public health data. Consent—in strictly legal terms—is often provided for a specific purpose (e.g. for participation in research or release of information for clinical care). Children are legally unable to consent to data sharing beyond the traditional exchange of information between their family and clinical team, thereby accentuating their situational vulnerability and reinforcing their need for special protections. We draw on established guidelines related to pediatric research and clinical care to the extent that they pro- vide a conceptual basis for the child's best interests and respect the child's evolving decision-making capacities and rights.[5-8]

Data Sharing Involving Children: A Practical Policy Need

Despite ethical and scientific imperatives to share data, many existing data security and interoperability platforms are ill equipped to manage the volume and integrity of sensitive pediatric data.[9,10] Material and human resources for pediatric data sharing are also not typically accommodated in clinical budgets. Moreover, existing ethical-legal guidance for genomic and

associated clinical data sharing focuses primarily on consenting adults.[11,12] Taken together, competing notions of (informational) risk and benefit,[13,14] inadequate data infrastructures (eg, data storage, management, interoperability, and security),[15] and the complexities of proxy consent to access children's data[16-18] limit many of the clinical advancements that broad data sharing in pediatrics could harness.

This article thus fills a gap at the nexus of ethical, legal, and scientific policies guiding pediatric data sharing. We discuss how and why enabling access to pediatric genomic and associated clinical data is beneficial to current and future patients. We contend that those who generate such pediatric data have a duty to extend to children and their families the opportunity to share those data. These and other considerations comprise 10 policy points to consider we outline for sharing genomic and associated clinical data involving pediatric patients. Our points pay special attention to data sharing in a clinical context, yet also address the blurring of traditional distinctions between genomic and associated clinical data generated within the learning health care system.[19] Initial points of the Key Implications for Data Sharing (KIDS) framework were developed based on a systematic review of reasons drawing on the data sharing literature (V. Rahimzadeh, MSc, unpublished data, February 2018), and were subsequently refined at a consensus working group meeting during the 4th Plenary of the Global Alliance for Genomics and Health held in October 2016. Our points are complementary to the Frame- work for Responsible Sharing of Genomic and Health-Related Data of the Global Alliance for Genomics and Health,[20] and as such constitute a living document that we anticipate will evolve in parallel with contemporary advances in the field of pediatric genomics.

Toward a Data Sharing Practice and Culture

The following risk-benefit factors anchor our points to consider (Box 1) for sharing individual as well as population data involving children: maximizing potential medical benefit for the individual pediatric patient whose data are shared; maximizing potential benefit for the patient's family; maximizing potential benefit for other pediatric patients; and protecting data privacy and security for children and their relatives. Each point to consider and its practical implications for pediatric patients are discussed in further detail in the subsequent sections.

Box 1. Key Implications of Data Sharing (KIDS) in pediatric genomics: policy points to consider for **KIDS**

Children's Involvement

- The best interests of children are primary
- Children should be listened to and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways

Parental consent

- Parents should be informed in a transparent manner how information regarding their child will be securely managed and used. In a research context, data sharing infrastructures should enable children to withdraw consent when possible on reaching the age of majority
- Parental authorization for ongoing or future unspecified research should include the provision of information related to existing data governance
- Values conveyed by family, legal guardians, or primary caregivers should be respected when possible

Balancing Benefits and Risks

- All health care professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent
- The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits

Data protection and release

- Duplicative collection of research data involving pediatric patients should be avoided
- Anonymized pediatric data should be made available via publicly accessible databases. Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process
- Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data

Children's Involvement

The best interests of children are primary (Box 1). Linked genomic and associated clinical data can directly benefit a child when comparison of disease-specific genomic regions with those of other individuals in a variant reference database leads to the diagnosis or exclusion of serious disease in the child.[21] Other and future children benefit indirectly from the contributions of data from children before them when those data assist in the analysis of their own genomes and exomes. The concept of "benefit to family" as a result of sharing results of genomic testing in the child has also been defended as a derivative of the benefit to the child.[22] Sharing data from a patient's sibling(s) or other biologically related relative, for example, may be clinically useful for treating or monitoring an affected sibling who is as-yet asymptomatic. More recent discussions in the literature have centered on the extent to which biological relatives assume informational risk when family members make

their genomic information public for clinical purposes or other- wise, and whether consent should be obtained from those biological relatives as well.[23]

Pediatric data sharing coheres with best interests standards that are codified in international conventions[5-8] insofar as such sharing leads to improved treatment of children (eg, enabling diagnosis or identifying optimal therapeutic targets). We propose data sharing as one mechanism to address knowledge gaps in understanding possible genomic causes of childhood disease but recognize that sharing alone cannot overcome all limitations therein. More data and analysis of phenotype-genotype correlations are needed to reduce the risks of genomic misinterpretation or misattribution that impede accurate diagnosis and optimal treatment. The aforementioned circumstances underscore the combined situational and clinical complexity of deciding whether data sharing is indeed within a child's best interest. The working group thus noted that "best interests" are necessarily contextual and individualistic in all cases. Shared decisions to contribute pediatric data should be based on a tripartite relationship of mutual trust between patients, families, and health care teams.[24]

Children should be listened to and involved in developmentally appropriate ways in the decision-making processes related to genomic and associated clinical data sharing (Box 1). Children's decision-making capacities evolve as they mature. Involving children where appropriate in shared decision making fulfills the principle of respect for persons by acknowledging their agency. The United Nations Convention on the Rights to the Child protects this "right to be heard" under Article 12.[8] Until the child is able to legally consent fully, assent should be obtained when appropriate and feasible. Assent procedures should deliver child-friendly and developmentally appropriate explanations of the nature, purpose, and implications of data sharing commensurate with the child's level of understanding. Indeed, assent for data sharing or other clinical decisions may not always be possible or appropriate, such as for neo- nates or developmentally immature children, or for those with severe mental or physical disabilities that limit communication. Changes in a child's maturity thereby warrant alternate approaches to engage children in discussions about data sharing in partnership with parents and their health care teams. Recontacting children once they reach adulthood to obtain their consent for ongoing use of their data respectfully shifts the primary locus of decision making in line with children's evolving maturity.

Parents should be informed in a transparent manner how in- formation regarding their child will be securely managed and used. In a research context, data sharing infrastructures should enable children to withdraw consent when possible on reaching the age of majority (Box 1).

Although parents or legal guardians consent on behalf of their children to share data, it is recommended that children make their own decisions regarding data sharing when their capacity is legally recognized. Recontacting children at the age of majority enables them to exercise this future capacity,[25] but the logistical challenges, scope of parental authority, and justification for recontact is widely debated in the literature.[26-29] Working group members considered the child's right to information and data withdrawal at the age of majority to be an ethically meaningful practice that should be strengthened when logistically possible. Members also emphasized how clinical contexts differ significantly from the research con- text in this regard. Depositing anonymized pediatric data in an aggregated database prevents reidentification of the child, but also significantly reduces the ability to withdraw the child's data if the child opts to do so on reaching adulthood. Other members of the working group prioritized the decisional rights of families. The working group proposed a notification system with the ability to opt out for minors on reaching adulthood (legal or presumed).

Both the American College of Medical Genetics and Genomics[30] and Statistics Canada[26] endorse such systems for use in longitudinal as well as pediatric biobank studies.[31] Recontact with notification of the opportunity to opt out might involve a survey reminding the now- adult participants of the terms of data sharing their parents consented to on their behalf and stipulating how they can withdraw, if applicable. The research team should seek a waiver from the appropriate research ethics committee if recontact is not possible or feasible, which may the be the case for some longitudinal studies that depend on data collection, analysis, and sharing throughout the child's life.[26] The waiver achieves the following 2 aims: (1) allows children the right to withdraw and (2) enables continuous sharing of children's data with the same security and safeguards without explicit recontact or reconsent at the age of majority.

Parental Consent

Parental authorization for ongoing or future unspecified research should also include the provision of information related to governance of existing data (Box 1). Parents must be adequately in- formed of the nature, scope, and actual and anticipated implications of sharing their child's data to make an informed decision about whether this is indeed in their child's best interest. Although the direct and indirect clinical benefits of pediatric data sharing are demonstrable, once publicly released, genomic data "is virtually impossible to retrieve or to make it private again."[32(p22)] In particular, the working group debated whether parents should be authorized to consent broadly to sharing their child's data in open access databases.[33,34] Members agreed that parents and families should be apprised of the

governance mechanisms to keep their child's data secure. Parents should be informed of the possibility that their child's data may be irretrievable (and hence unable to be withdrawn) if the data are shared anonymously or aggregated. Governance mechanisms include appropriate ethics review of some future, unspecified research projects, as well as where and with whom the data could potentially be shared.

Values conveyed by family, legal guardians, or primary care- givers should be respected when possible (Box 1). The informed con- sent process should be sensitive to the cultural background and preferences of the family. Parents or legal guardians may have specific questions, informational needs, doubts, and preferences based on their social background, cultural, religious, or personal values.[35,36] These should be respected during communication with parents and other family members and taken into consideration when sharing sensitive associated clinical data.

Balancing Benefits and Risks

All professionals involved in data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent (Box 1). Direct clinical benefits from sharing pediatric data are contingent on the type of data shared, the database within which these data are deposited, and the terms of access to the data. All professionals involved in sharing pediatric data have a responsibility to discuss with parents what realistic benefits and risks are anticipated prior to data contribution. The greatest direct clinical benefit anticipated is to an individual patient who accesses data that laboratories and health care professionals (and occasionally the patients themselves) share to interpret the patient's sequencing results. Consider, for example, databases that contain genome-wide sequencing data from patients with disease phenotypes likely to be, but not previously, associated with a known causal mutation. The first data contributors do not benefit directly until data from others with the same genotype and phenotype accumulate. Notwithstanding the benefit to patients with rare diseases, earlier data contributors benefit when a robust number of cases accrue in the database that support the genotype-phenotype correlations of interest. Sharing a patient's data using tools such as DECIPHER (Database of Genomic Variation and Phenotype in Humans Using Ensembl Resources)—a database of un- known variants or those suspected to be pathogenic in patients with abnormal phenotypes—can achieve the type of diagnostic benefit described.[37]

The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits (Box 1). Appropriate weight should be given to benefits and risks that are supported by empirical evidence. A proportionate risk assessment for sharing pediatric data should be premised on the nature, likelihood, and magnitude of the informational

risks anticipated using existing approaches described in the literature.[38] Although the public reports fears of unauthorized access, data breaches, and deidentification of their child's genomic data, such events are few.[39-41] Implicit in our discussion is that using and sharing pediatric data necessarily involves informational risks. Methods for securing data, reducing the potential for identifiability, and improving interoperability (and, by extension, the analytical quality) together improve the benefit-risk calculus for pediatric data sharing that we elaborate below.

Data Privacy, Identifiability, and Interoperability

Privacy is both value laden and contextual, and is best protected through explicit anonymization. Although many families prioritize strict privacy of health information (eg, diagnosis, treatment, and prognosis), others may make privacy tradeoffs to obtain richer di- agnostic information. This scenario can be particularly true of families of children with rare genetic disorders, who often freely share their child's medical information, including on social media.[42] Anonymization may be feasible when, for example, these data are limited to a recurrent variant in a single gene and the phenotype is relatively common. Because the richness of genomic or rare dis- ease phenotypic data inherently bears the potential to reidentify individuals, total anonymity can never be guaranteed. The potential for identification increases when genomic data are linked with other data sources, including phenotype, familial, and other sociodemographic information. Without associated phenotypes, however, genomic variant data are often not interpretable in a clinical context. Yet, it is the very association of genotypic and phenotypic data that introduces an ethical tension between direct clinical benefit to the child or enhanced research value and data security. Considering these tensions, the working group adopted the position that security standards for pediatric data sharing correspond to the nature and quality of the data needed to generate the best available clinical interpretation, as well as its potential for reidentification. The Data Sharing Lexicon[43] outlines the terminologies and data securities to which we refer (Box 2).

Box 2. Relevant Lexicon of Methods to Strip Data of Identifying Information[43]

- Anonymization: The irreversible delinking of identifying information from associated data.
- Deidentification: The removal or alteration of any data that identify an individual or could, foreseeably, identify an individual in the future.
- Encryption: A mechanism of safeguarding stored data or information by making those data or information unreadable without access to the correct decryption method.

- Pseudonymization or coding: The act of replacing an identifier with a code for the purpose of avoiding direct identification of the participant, except by persons holding the key linking the code and identifier.

Data Protection and Release Requirements

Reasonable efforts should be taken to avoid unnecessary, repetitive, and duplicate data collection if adequate data exist and are readily available (Box 1). Our points to consider take as foundational the idea that data should be shared rather than kept private or redundantly recollected. Pediatric data could be justifiably recollected if they answer a new research or clinical question, improve the sensitivity or specificity of genomic tests, or otherwise augment the quality of existing data. In other words, children should not be exposed to added informational risk if similar data were already collected. It is the responsibility of researchers, health care professionals, and others generating pediatric data to share the data responsibly in accordance with relevant laws and the points to consider proposed herein.

Anonymized pediatric data should be made available via publicly accessible databases. Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process (Box 1). Data access controls are among the many practical means for ensuring data security commensurate with the sensitivity of linked phenotypic and genotypic data. Requirements for data privacy and security are not only enforced using institutional policies but are also stipulated by local, national, and international law. Three primary access mechanisms are discussed in the literature.[44] Anonymized pediatric data that are irreversibly delinked and have no reason- able likelihood of reidentification (Box 2) should be made publicly available in large shared databases. Given the possibility of reidentification for linked genomic and associated clinical data, the working group recommended that sensitive or potentially identifying data involving children should be stored in databases or archives under controlled or registered access regimes.

How controlled access databases will manage greater linkage of clinical data has not yet been explored in depth. The working group proposed that data custodians who physically share data should be charged with conducting an overall data sensitivity evaluation that takes into account the combination of all data sets in which data have been shared.[45] Data users, in turn, are responsible for complying with the data security and privacy standards as stipulated by law in the jurisdiction in which the data were generated.

Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data (Box 1). Pediatric data sharing conducted in

the spirit of improved diagnosis and good professional practice should be a tie that binds clinical research, pediatric care, and public health. We contend that the direct and indirect benefits described through- out this article tip the benefit-risk balance in favor of promoting more concerted data sharing in the pediatric clinic to, among other reasons, enhance intragenerational solidarity[46] and foster better patient care within learning health care systems. The working group defends an ethical duty among clinical laboratories, physicians, and other health care professionals to offer children and their parents the opportunity to share pediatric genomic and associated clinical data pursuant to these direct and indirect benefits.

Conclusions

It is our intent that all children benefit from the sharing of pediatric genomic and associated clinical data; such sharing requires stake- holder cooperation across the clinical translational continuum. Considering its potential for both immediate and future clinical benefit, sharing of anonymized data could be considered a public health good not unlike newborn screening. These points to consider offer a platform from which to launch a stronger commitment to collabo- ration through data sharing across stakeholder communities.

Future research will need to address implementation barriers and facilitators of the data sharing practices and responsibilities out- lined herein (in particular, the accountability of clinical laboratories). Underrepresentation in genomic databases among children of racial and ethnic minorities, as well as children from low-income countries, is becoming a pressing ethical and scientific concern.[47] At present, the practical policy points we offer aim to ensure that pediatric genomic data sharing is the norm rather than the exception, and that benefiting children remains at the forefront of genomic innovation.

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Preface to Chapter 5 [Manuscript 4 to be published in a health policy or technological forecasting journal]

A modified Delphi study according to Lindstone and Turoff was adopted to answer Research Question **II**: *how do Canadian pediatricians, genomic researchers, ethicists and bioethical scholars prioritize the ethical-legal, social and scientific factors of genomic and associated clinical data sharing involving children in Canada?* The strengths of the policy Delphi towards assessing multi-stakeholder values and positions on genomic and associated data sharing involving children— a policy issue currently in a negotiatory state (Hart and Kleiboer 1995)—substantiated this methodological choice. The synthesis of findings from the systematic review of reasons detailed in Chapter 2, as well as input from key informants from the Paediatric Task Team of the Global Alliance of Genomics and Health presented in Chapter 4 together achieved Phases 1 and 2 of the policy Delphi: formulation of the policy issue and exposing the options, respectively. Results from Phases 3-6 are presented in Chapter 5—determining initial positions on the policy issue, exploring and obtaining reasons for disagreements, evaluating the underlying reasons, re-evaluating the options. They were achieved following three iterative rounds of online surveys involving pediatric data sharing stakeholders in Canada.

V. Rahimzadeh was responsible for the protocol design, ethics review board submission and annual renewals, participant recruitment, survey design, data collection and analysis, and preparation of the manuscript in Chapter 5. A dedicated project website was also created to enable public accessibility to, and verification of raw study data during all phases of the policy Delphi study (www.projectpedigree.org). The website served as a central platform for disseminating study-related publications, news of upcoming conference presentations where results were shared, and all requisite ethics certificates and informed consent documents to ensure transparency and compliance with CIHR funding guidelines.

Thesis supervisors GB and BMK advised on appropriate survey measures and reviewed analytical findings after each Delphi round. Thesis committee member A. Issa piloted surveys and provided feedback on survey design for Rounds 2 and 3. Data and analyses presented in Chapter 5 will be submitted to a health policy or technological forecasting journal upon successful completion of all doctoral requirements.

CHAPTER 5 [Manuscript 4]

Cloudy With A Chance Of Data: Forecasting Ethical-Legal Considerations Of Sharing Pediatric Genomic And Associated Clinical Data

V. Rahimzadeh, BM Knoppers, G. Bartlett

Abstract

The informational feedback loops driving clinical progress in genomics-enabled learning healthcare systems rely on the production, access and exchange of genomic and associated clinical data. The ethical-legal considerations of such production, access and exchange can be accentuated when data involve children based in part on tensions between their consent-related vulnerabilities and uncertain informational risks. A systematic review of reasons of the empirical and grey policy literature informed the Key Implications of Data Sharing (KIDS) framework for pediatric genomics published elsewhere. Its jurisdictional applicability in the Canadian context was the focus of a three-round policy Delphi study reported in this article, which was designed to assess areas of consensus and dissent that may be relevant for the framework's broader adoption in Canada. Thematic content, and descriptive statistical analyses were used to investigate how 12 Canadian pediatricians, genomic researchers, ethicists and bioethics scholars prioritized the policy positions outlined in the KIDS framework. The Delphi panel reached consensus on 9 of 12 original policy positions using statistical thresholds proposed by de Loe (1995). An additional position regarding return of clinically actionable genomic findings was suggested after Round 1 and subsequently achieved consensus. Discrepant views related to informational risks, data access and oversight of anonymized versus coded genomic data were primary sources of dissent for related positions outlined in the KIDS framework. This policy Delphi suggests that skepticism of data anonymization drives support for more stringent access controls and oversight of genomic and associated clinical data when they involve children.

Introduction

Informational feedback loops driving clinical progress in the genomics-enabled learning health system rely on the production, use and exchange of data, including from children. Both policy and technical data infrastructures are required to optimize these loops, the former of which are the markedly limited in the pediatric genomics space and the focus of this article. Despite the research-care nexus that genomics-enabled learning health systems afford in understanding possible etiologies of pediatric diseases, the respective ethical-legal traditions circumscribing appropriate oversight of data sharing in clinical research and care remain separate and distinct. The need for such policy-practice coherence in genomic data sharing can be accentuated when involving children—and potentially for unborn children as well (Pormeister and Drożdżowski 2018). While their data may require special protections (Lewis, Bonhomme, and Bloss 2018), children's diagnosis may also depend on wider accessibility to genomic data (Schofield et al. 2018).

Provincial jurisdiction over healthcare spending and research make Canada a unique national context in which to study scientific collaboration vis-à-vis genomic data sharing. As technical capacities evolve to support more sophisticated genomic analyses, so too are governance bodies responsible for evolving professional competencies that enable them to appropriately review pediatric research protocols involving genomic data sharing. Furthermore, national guidelines for research involving humans are not federally binding in Canada except for researchers who receive federal funding, or for researchers whose institutions mandate adherence to national ethics guidelines (Canadian Institutes of Health Research Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada. 2014).

This article presents results from a policy Delphi study that aimed to validate an ethical-legal framework for responsible sharing of genomic and associated clinical data involving children. It assessed the relative importance, feasibility, desirability and confidence of policy points to consider outlined in the Key Implications of Data Sharing (KIDS) framework (Rahimzadeh et al. 2018) for applicability in the Canadian pediatric genomics context, specifically. The study identified areas of consensus and dissent on individual policy positions from the perspectives of Canadian data sharing stakeholders. While the KIDS framework considered ethical-legal and social (ELSI) factors that enable responsible data sharing internationally, its jurisdiction-specific implementation has not yet been explored for complementarity with existing research, clinical and health data protection regulations in Canada.

A policy Delphi according Turoff (1970) provides one methodological approach for filling this knowledge gap. The article begins by providing an overview of the research ethics challenges and scientific opportunities for precision medicine in pediatrics in the wake of the Human Genome

Project. It describes emerging models for precision medicine delivery with a focus on systems that embed genomic research and quality improvement/assurance directly into the patient care experience.

The learning health system—and specifically the *genomics-enabled* learning health system—is one such model. Data of considerable volume and varieties are needed to optimize genomics-enabled learning health systems, however, placing new demands on institutions to develop data policy and technical infrastructures. Recent data security breaches within and outside the healthcare sector have, however, jeopardized public trust in both types of infrastructures. Waning public trust signals a pressing need for scientific, clinical and patient communities to collectively negotiate norms of data privacy and security as they relate to advancing public projects like genomic science.

A 3-round policy Delphi was designed to initiate this policy negotiation in the Canadian context by assessing an ethical-legal framework for data sharing involving children. Such a framework is one policy pillar upon which genomics-enabled learning health system can build to improve standards of care for Canadian children and their families.

Healthcare systems that learn

"Care that is important is not delivered. Care that is delivered is often not important" (Institute of Medicine. Ed. Olsen LA, Aisner D, McGinnis JM 2007). It was in response to this growing realization that the then Institute of Medicine's (IOM) Roundtable on Evidence-based Medicine was convened to find systems-based solutions to medical error, rising healthcare expenditures and missed opportunities to harness the analytical power of health information technologies. Re-imagining health systems as centers of service delivery and hubs for clinical innovation was the foundation for what the IOM proposed as a learning health system (LHS), and later a genomics-enabled learning health system (GeLHS) (Beachy, Olson, and Berger 2015). Both systems share a central tenet: to prioritize the availability and systematic uptake of timely clinical evidence that can directly inform patient care. GeLHS builds on these, and other foundational guidance for the learning health system (Faden et al. 2013) with a specific focus on improving the integration of genomics into patient care delivery.

Priority planning centered on learning health systems and genomics have since launched as part of national initiatives across the world (Stark et al. 2019), and in Canada under the Pan-Canadian Strategy for Patient Oriented Research Network in Primary an Integrated Health Care Innovations (2019), as well as the Canadian Institute for Health Services and Policy Research Strategic Plan for 2015-2019 (Canadian Institutes of Health Research 2016). This dedicated federal

funding is indicative of general support for the general mission and philosophy of learning health systems, but also of the operational challenges institutions face in realizing them. For learning health systems generally, and GeLHS specifically, the most formidable challenges identified in Canadian national strategies are data sharing related (Lavis et al., n.d.). Given the complexity of gene-gene and gene-environment interactions, genomic and associated data sharing are simultaneous scientific and ethical imperatives[xix]. Incorporating results from whole genome- and exome sequencing and associated clinical data into a child's medical record, for example, inevitably complicates the technical infrastructures needed to render such linkages secure, and at the same time useful for pediatricians and researchers alike (Zhou et al. 2016; Larson and Wilke 2015). What's more, this linkage implies that health practitioners are genomic data 'literate' in translating genomic information into clinical action.

A pediatric focus for GeLHS

The above themes exemplify the complex data ecosystems and operational intricacies of a genomics-enabled learning healthcare system (Krumholz 2014) that treats genomic research as a "natural outgrowth and product of the healthcare delivery process" (Institute of Medicine. Ed. Olsen LA, Aisner D, McGinnis JM 2007). Children are increasingly becoming an important patient population from which the healthcare system can learn in this regard (C. B. Forrest et al. 2014) because many rare genetic, and other heritable conditions are unique to children and may present early in life (Hastings and Dixit 2019). Such understandings cannot therefore be extrapolated from the generation, analysis and exchange of data involving adults. The policies and practices guiding proportionate governance of genomic data production, access and exchange are, however, markedly limited in the pediatric genomics space (Bennett et al. 2019). Enhancing opportunities for children and families to share their data is critical to genomic data production (Ferrer et al. 2019; S. J. Forrest, Geoerger, and Janeway 2018), and calls for need to support researcher-clinician collaboration.

[xix] One workshop attendee featured in the 2015 IOM report likened data sharing to organ donation, advocating for a culture that recognizes how "in terms of discovery and integration and learning health systems, nothing is more important culturally than for society to understand the importance of data sharing."

Neither researchers nor clinicians alone can generate enough data to make sound statistical associations between the child's genome, optimal treatments and population health outcomes. Genomic data is hence sourced from both clinical and research environments. Despite their combined utility for understanding etiologies of pediatric disease in the GeLHS (Wright et al. 2019), ethical-legal permissions for use of, and access to these data are under separate regulatory purviews. Unlike clinical care, research that involves children—like research involving all humans—requires ethics oversight. (Ge)LHS inevitably frustrate this regulatory distinction as Grudniewicz et al confirm: "Developing a framework [for the learning health system] confronts the distinction between clinical research and clinical practice in terms of ethics, since the use of identifiable patient data for continuous learning within a LHS—that may involve several health providers—is neither a recognized form of clinical research nor routine use for clinical practice such as physician-patient encounters." The authors go on to note that "Integrating patient data collected at the point of care with population-based research data is thus difficult to accomplish given existing ethical guidelines regarding patient privacy and data security" (Lessard et al. 2017).

Lastly, quality data beget quality analytics. The former requires appropriate storage and management while interoperable platforms for data exchange support the latter. The need to facilitate policy-practice coherence in genomic data production, use and exchange can be accentuated when involving populations such as children (Bennett et al. 2019), for whom such data may require special protections. This study makes the needed policy-practice links using policy Delphi methods to formulate an ethical-legal framework that can support responsible genomic and associated clinical data sharing involving children in Canada. The design and results from a three-round policy Delphi are described in detail in the subsequent sections.

Methods

Policy Delphi Design

The framework formulation objective of this study substantiated a methodological approach that could elicit critical views on policy options among a group of informed stakeholders in pediatric data sharing. A modified Delphi study, the policy Delphi, was therefore adopted to answer *how do Canadian pediatricians, genomic researchers, ethicists and bioethical scholars prioritize the ethical-legal, social and scientific factors of genomic and associated clinical data sharing involving children in Canada?* The policy Delphi is an "iterative polling technique" (Baker and Moon 2010), and departs from the conventional Delphi on several accounts. Namely, policy Delphi studies emphasize underlying rationales for consensus and dissent on policy issues, rather than to facilitate decision-making per se. First proposed by

Turoff in 1970, the policy Delphi is an "organized method for correlating views and information pertaining to a specific policy area and for allowing the respondents representing such views and information the opportunity to react to and assess differing viewpoints"(M Turoff 1970, 83). Whereas the chief aim of conventional Delphi studies is to reach consensus, the policy Delphi seeks to entertain a comprehensive, albeit not exhaustive, suite of policy options; to estimate the impact and outcomes of a particular option; and to examine and estimate the acceptability of any particular option (M Turoff 1970, 83). This orientation towards informant engagement on policies issues that Hart and Kleiboer define as in 'negotiatory states' (1995) further substantiated the policy Delphi as a useful methodological choice.

Despite the differences in Delphi traditions, Baker and Moon (2010) propose that all Delphi studies adhere to four key principles of anonymity, asynchronicity, controlled feedback and statistical response. Anonymity purports to reduce imbalances in power that can often restrict honest feedback when solicited in a group setting, particularly when members vary in seniority. An online platform can facilitate anonymity in this regard and was therefore used in this study. The iterative nature of study procedures makes the policy Delphi asynchronous, enabling panelists to determine when and how they choose to provide feedback. This feedback is systematically collected and analyzed, then used to inform subsequent rounds of the policy Delphi that recapitulate the results to panelists in a controlled way. Panelists provide their feedback primarily in quantitative forms that are often supplemented with opportunities to qualify this feedback qualitatively in written responses.

The structure of the communication process and careful panel selection together enhance the richness of informed views the policy Delphi is poised to generate. The policy Delphi has to date has been used to structure policy discussions and formulate frameworks in myriad public policy sectors such as education (Adam Manley 2013), resource management and energy (Baumann, Ervin, and Reynolds 1982; Klenk and Hickey 2012; McGeoch, Brunetto, and Brown 2014), foreign affairs (Smit and Mason 1990) and city planning (Yau and Chiu 2015). Its application to genomics has, in contrast, been limited (Messner et al. 2016) and a unique contribution this study attempts to make.

Structure of the policy Delphi process

The above four principles were achieved in this 3-round policy Delphi through a structured communication process that Turoff (1970) outlines by I) formulating the policy issue, II) exploring the options, III) determining initial positions, IV) exploring reasons, V) evaluating underlying reasons, and finally VI) re-evaluating options (**Figure 3**). An initial set of policy positions and goals for the proposed data sharing framework were formulated prior to the first round of the policy

Delphi. A systematic review of reasons and key informant committee meeting of the Paediatric Task Team of the Global Alliance of Genomics and Health were combined to fulfill phases I and II. They together informed the Key Implications of Data Sharing (KIDS) framework for pediatric genomics published elsewhere (Rahimzadeh et al. 2018) and to which panelists in this study responded. Thirteen key informants representing international stakeholder groups related to pediatric data sharing participated in this committee meeting as part of the 4th Plenary of the Global Alliance for Genomics and Health in Vancouver (CA) on October 16, 2016 (**Table 9).**

Figure 3. Policy Delphi procedures

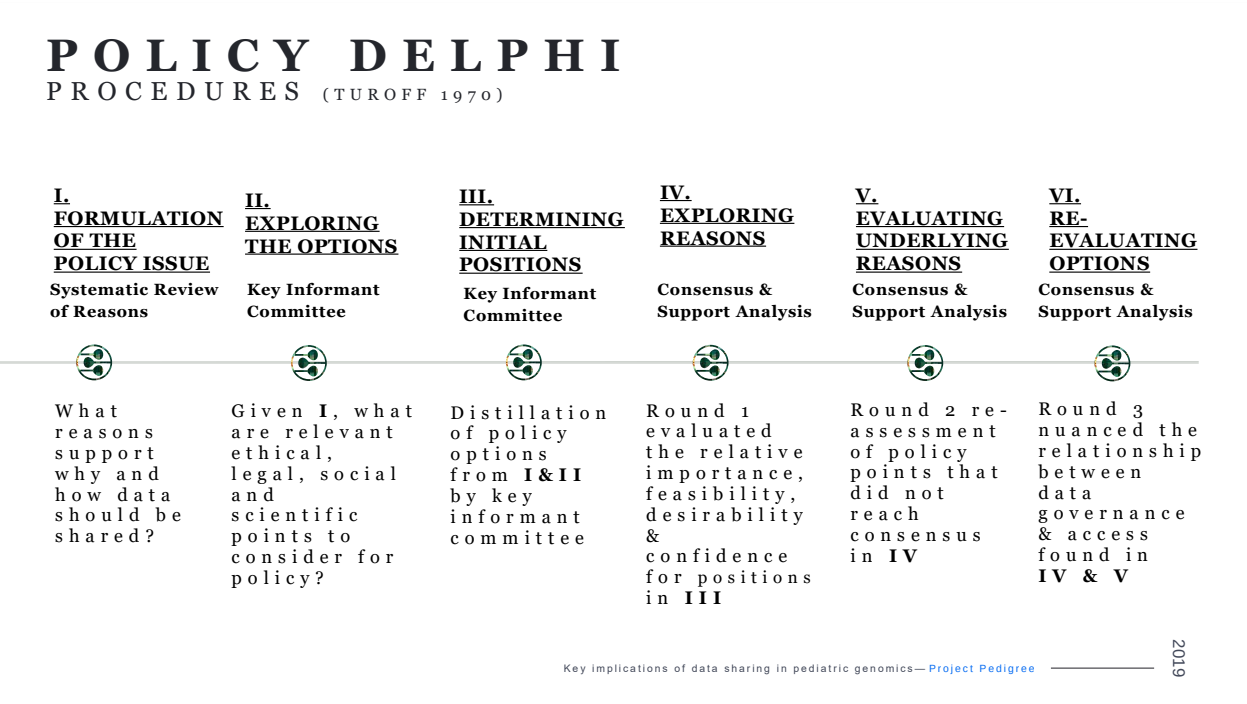


Table 9. Descriptive and demographic characteristics of key informant committee members from the Paediatric Task Team of the Global Alliance for Genomics and Health.

	USA	Canada	EU	Japan
Data sharing stakeholder group				
Medical genetics (pediatrics)	3		1	
Nursing	1			
Genomics ELSI scholar		4	1	1

Genomics funding agency	1			
Patient advocate	1			

Results from Phases III-VI—determining initial positions on the policy issue, exploring and obtaining reasons for disagreements, evaluating the underlying reasons, re-evaluating the options—are reported in this paper.

The initial positions of the KIDS framework were presented to a Canadian for review during the first two Rounds of this policy Delphi, while open-ended questions allowed panelists to formulate additional policy positions with supporting rationales. Their responses were also used to evaluate reasons for dissent whenever a proposed policy position received weak support or especially low ratings. Three or more individuals piloted each Round of surveys for comprehension, format and clarity prior to data collection.

In Round 1, a classification system according to consensus rankings and support was used to assess the relative importance, feasibility, desirability and confidence of individual policy positions outlined in the KIDS framework using a 4-point Likert Scale[xx]. The decision to use a 4-point rating system forced panelists to take a definitive position on the statements under review, either positively or negatively (Mitroff and Turoff 2002). Panelists were furthermore required to provide written rationales for their ratings to enable qualitative analysis of consensus and dissension points. Descriptive statistics derived from Likert ratings (M Turoff 1970) together with qualitative content analysis (Sandelowski 2000) of panelists' written responses helped benchmark "whether the group supported, opposed, or was ambivalent towards an option; whether the group was split…or whether no clear picture of support emerged" (de Loe 1995, 61) with respect to the policy positions evaluated in the KIDS framework.

Individual policy positions were retained for review in Round 2 if they resulted in 1) low consensus, 2) high polarity and/or 3) strong- to weak opposition. Therefore, policy positions that indicated high consensus, low to no polarity and strong support according to numerical thresholds and qualitative rationales were considered validated. All descriptive statistics and qualitative text data were analyzed in Microsoft Excel. The consensus and support system applied a consistent set of rules for analyzing ratings, in which the median and IQR was used to summarize the degree of

[xx] **Rating of 1** = very desirable /definitely feasible/ very important/ confident; **Rating of 2** = desirable /possibly feasible/ somewhat important/ reliable; **Rating of 3** = undesirable /possibly not feasible/ somewhat unimportant/ risky; **Rating of 4** = very undesirable /definitely not feasible/ very unimportant/ unreliable.

support and spread in the distribution, respectively, to screen those policy positions that should be retained for re-assessment in subsequent rounds. Criteria for consensus, polarity and support are provided in the supplementary materials. Because identifying the ELSI themes in panelists' arguments was the objective of this policy Delphi, numerical thresholds served as proxy indicators, rather than determinations of consensus and dissension.

In Round 2, panelists were provided a consolidated report of all ratings and qualitative rationales from Round 1. They reassessed their initial positions and re-rated policy statements retained from Round 1 on the basis of failed consensus, high polarization and strong- to weak opposition using the same 4-point Likert scale.

The third and final Round of the policy Delphi sought to disentangle relationships between appropriate data access and type of genomic data shared e.g. anonoymized vs. coded, and to confirm upon whom genomic data management and security responsibilities for children should rest in the Canadian pediatric genomics context. The final results from the Delphi, including the validated framework were distributed to panelists via a publicly accessible project website (www.projectpedigree.org).

Policy Delphi Panel

An expert panel should reflect diverse, yet well-informed perspectives on the policy issue of interest (Meskell et al. 2013). A typical sample size for the policy Delphi can range from 10-50 panelists in accordance with the study purpose, the complexity of the policy issue and realm of expertise required (Murray Turoff 2002; Mitroff and Turoff 2002; Rayens and Hahn 2000; de Loe 1995). Selection of members for the panel in this study followed recommendations from Needham and de Loë (1990). Panelists thus represented the experiences of targeted populations—practitioners and researchers sharing genomic and associated clinical data—and those with relevant authority in the policy field—data oversight committees and regulators.

The policy Delphi panel reflected a maximum variation sample of pediatric data sharing stakeholders with varied professional expertise in pediatric medicine, bioethics, research ethics, and genomic research. The panel further reflected a geographically representative sample, considering panelists were recruited from each of the 4 highest-grossing provinces in federal funding for pediatric genomics research in Canada (**Table 10**). Genome Canada launched the first Large-Scale Applied Research Project Competition centered on personalized medicine in May 2010, and a second competition in 2012. Both competitions funded pan-Canadian projects that uncovered "how genomics-based research can contribute to a more evidence-based approach to health and

improving the cost-effectiveness of the health-care system" (Canada 2015). Seventeen GAPH projects were funded across both competitions, 6 of which were specific to studying pediatric disease. Lead clinician-investigators from these 6 pediatric-specific projects were recruited, as well as the ethics board chairs involved in reviewing these projects across Canada.

Table 10. Descriptive and demographic characteristics of policy Delphi panelists over Rounds 1-3

Panel demographics	**No. of panelists**		
	Round 1 (n = 10)	**Round 2 (n = 12)**	**Round 3 (n = 12[xxi])**
Gender			
Male	6	7	6
Female	4	5	6
Province			
Quebec	2	4	4
Ontario	4	4	4
British Columbia	2	2	2
Nova Scotia	1	1	1
Alberta	1	1	1
Profession			
Clinician scientist	6	7	6
Genomics ELSI researcher	1	1	2
Law	-	1	1
REB Chair	2	2	2
Clinical ethicist	1	1	1

Panelists were invited to participate if they were involved in a GAPH project that:

- Focused on diseases affecting children or adolescents (newborns to age 18)
- Pan-Canadian
- Obtained approval, or was in the process of obtaining ethics approval from an board using a single review board model
- Involved the collection, use and distribution of sequence data and/or biological samples from children from both clinical and research settings

Data collection

[xxi] While 12 panelists participated in Round 3, only complete survey data were reported in the analysis.

All data was collected from Jan-October 2018. Specific data collection timelines for each phase of the policy Delphi study are presented in **Table 11.** A total of 40 invitations were sent to participants who met the inclusion criteria. Data from 10 panelists were collected in Round 1, 12 in Round 2, and 10 in Round 3[xxii]. The overall response rates were 25%, 30% and 25%, respectively.

Table 11. Data collection timeline for the KIDS policy Delphi

Policy Delphi phase	Activity	Data collection timeline
Formulation of the policy issue—What is the issue that should be under consideration? How should it be stated? **Exposing the options**—Given the issue, what are the policy options available? **Determining initial positions on the issues**—Which are the ones everybody already agrees upon and which are the unimportant ones to be discarded? Which are the ones exhibiting disagreements among respondents?	Systematic Review of Reasons ↓ Key Informant Committee Meeting	April 2016 – September 2016 ↓ October 2016 – December 2017
Exploring and obtaining the reasons for disagreements—What underlying assumptions, views or facts are being used by the individuals to support their respective positions?	Round 1, policy Delphi	February 26, 2018 – April 8, 2018
Evaluating the underlying reasons—How does the group view the separate arguments used to defend various positions and how do they compare with one another on a relative issue?	Round 2, policy Delphi	May 16, 2018 – July 31, 2018
Re-evaluating the options—Re-evaluation is based upon the views of the underlying 'evidence' and the assessment of its relevance to each position taken	Round 3, policy Delphi	September 28, 2018 – November 6, 2018

[xxii] *infra* iii.

Results

Round 1

Evaluating the underlying reasons

Ten panelists participated in Round 1 (response rate 25%), and evaluated 12 policy statements related to pediatric genomic and associated clinical data involving children on the basis of 2 of the following 4 factors using a 4-point Likert scale: relative importance, feasibility, desirability and confidence (**Appendix B**). Six policy position statements (1-4, 8 and 9) achieved high consensus, and low to no polarity after Round 1, and were therefore not retained for further analysis in Round 2. Based on a segmentation analysis of ratings by panel member profession, research ethics review board chairs/members had the highest aggregate score total of any stakeholder in the panel—indicating lowest perceived relative importance, desirability, feasibility and confidence across the positions evaluated.

Exploring and obtaining the reasons for disagreement

Table 12 summarizes the dual ratings for each policy position statement, and provides descriptive statistics for consensus, polarity and support according to the parameters outlined in **Tables 6, 7** and **8**. Policy position Statements 1 and 3 ranked highest in terms of relative importance; ratings for relative importance concerning Statement 3 and desirability of Statement 4 tied for lowest overall polarity. Three statements achieved identical degrees of support across both ratings (2, 5 10), while five statements (1, 3, 6, 8, 11) differed in support by only one degree. Of the three statements that varied most in their degree of support across the two ratings (statements 7, 9, 12), only Statement 12 simultaneously indicated strong polarity. A combined average was also calculated across the two ratings for each policy position statement, and was then ranked in order of lowest average i.e. indicating most important, feasible, confident and desirable. **Table 13** provides these rankings.

Thematic content analysis of all qualitative rationales corroborated the statistical consensus and polarity measurements of panelists' ratings. An inductive approach to line-by-line coding of these qualitative reasons yielded summary codes that were then provided to panelists as part of the controlled feedback in Round 2. The coded reasons underlying degrees of support and opposition for each policy position are reported in **Table 14.**

Re-evaluating the options

Six statements were retained for re-assessment in Round 2 because their group ratings indicated i) low consensus and/or ii) weak to strong polarity. Three of the lowest-ranked statements for feasibility according to the descriptive statistics measures outlined in **Table 14** were also retained for re-assessment such to better understand the practical and theoretical reasons given for their perceived infeasibility. Panelists suggested 4 total amendments to existing policy position statements 7, 10, 11 and 12. Panelists requested changes to the wording in Statement 11, as well as removal of the option to access identifiable or coded pediatric data using a registered access process. Amendments to Statements 7 and 12 reflected substantive changes to the ethical-legal duties of professionals involved in data sharing consent.

Statement 7 should more specifically convey that the responsibility to balance potential benefits and risks rests solely with those professionals involved in data sharing consent processes, according to panelists' requests for amendments. Similarly, the amendment to Statement 12 reflected the opinion that only researchers should be held responsible for providing children and their families with the opportunity to share data. Several panelists recommended that Statement 10 be eliminated entirely from the KIDS framework, and panelists voted whether to eliminate, preserve, or further amend it during Round 2. One panelist recommended the following new statement for inclusion in the overall framework, which was subsequently evaluated in Round 2 as Statement 13: *Incidental (secondary) findings of clinically actionable, validated genomic results should be made available*. The identical 4-point Likert rating schema and scales used to evaluate statements in Round 1 were applied to evaluate Statement 13 in Round 2, and panelists were also prompted about whether to formally adopt Statement 13 into the overall KIDS framework.

Table 12. Summary results from Round 1 ratings of 12 policy position statements of the KIDS framework. Policy position statements in grey were retained for re-rating and re-assessment in Round 2.

	POLICY POSITION STATEMENT	MEASURE	RATING				AVERAGE	CONSENSUS	SUPPORT	POLARITY
			1	2	3	4				
1	The best interests of children are primary	Relative Importance	7	2	1	0	1.4	High	SS	None (0.488)
		Feasibility	2	6	2	0	2	High	ws	None (0.444)
2	Children should be listened to, and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways	Desirability	1	8	1	0	2	High	ws	None (0.222)
		Feasibility	0	7	3	0	2.3	High	ws	None (0.233)
3	Parents should be informed in a transparent manner how their child's genomic and associated clinical data will be securely managed and used.	Relative Importance	8	2	0	0	1.2	High	SS	None (0.177)
		Confidence	1	7	2	0	2.1	High	ws	None (0.322)
4	In a research context, data sharing infrastructures should enable children to withdraw consent to continued sharing of their genomic and associated clinical data when possible upon reaching the age of majority.	Desirability	2	8	0	0	1.8	High	ws	None (0.177)
		Feasibility	1	2	7	0	2.6	High	wo	None (0.488)
5	Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance.	Relative Importance	6	2	2	0	1.6	High	SS-ws	None (0.711)
		Desirability	5	4	0	1	1.7	High	SS-ws	Weak (0.9)
6	Values conveyed by family, legal guardians or primary care givers should be respected when possible.	Relative Importance	5	3	2	0	1.7	High	SS-ws	None (0.677)
		Feasibility	2	2	4	2	2.6	Low	—	Strong (1.155)
7	All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent.	Desirability	5	3	1	1	1.8	High	SS-ws	Weak (1.06)
		Feasibility	2	4	2	2	2.4	Low	—	None (0.5)
8	The decision to share pediatric genomic and associated clinical data should be supported by an	Feasibility	6	3	1	0	1.5	High	SS-ws	None (0.5)

	evaluation of realistic risks and benefits.	Confidence	4	5	1	0	1.7	High	SS-ws	None (0.455)
9	Duplicative collection of genomic research data involving pediatric patients should be avoided.	Desirability	6	3	1	0	1.5	High	SS-ws	None (0.5)
		Feasibility	0	7	2	1	2.4	High	ws	None (0.488)
10	Anonymized pediatric data should be made available via publicly accessible databases.	Desirability	4	3	2	1	2	High	SS-ws	Strong (1.11)
		Feasibility	3	4	3	0	2	High	—	None (0.66)
11	Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process.	Desirability	7	1	1	1	1.6	High	SS	Strong (1.115)
		Feasibility	4	5	0	1	1.8	High	SS-ws	Weak (0.844)
12	Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.	Desirability	4	3	2	1	2	High	SS-ws	Strong (1.11)
		Feasibility	3	2	4	1	2.3	Low	—	Strong (1.122)

Table 13. Qualitative reasons for support and opposition to 12 policy position statements during Round 1

ROUND 1 POLICY POSITION STATEMENT	MEASURE	REASONS FOR STRONG SUPPORT	REASONS FOR WEAK SUPPORT	REASONS FOR WEAK OPPOSITION	REASONS FOR STRONG OPPOSITION
The best interests of children are primary	Relative Importance (SS)	• It is a foundational principle in pediatric ethics • Children are vulnerable	• Must be balanced with other considerations • Are an inappropriately high standard for data sharing • Require resources to oversee	• The statement is empty if best interests are not defined	
	Feasibility (ws)	• Fulfilling best interests does not present implementation challenges when accompanied by oversight	• Resources are needed to adapt policy • Busy clinical teams may not be able to engage children in decisions • Disagreement between parent & child	• The best interests standard is inappropriate if sharing for the purposes of research • Providing clinically actionable findings	

			complicates ability to continued data sharing/use	when there is clear medical benefit is more feasible	
Children should be listened to, and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways	Desirability (ws)		• Additional human resources e.g. genetic counselling are needed to help understand & interpret genomic complexity • Benefits contingent on child's age, comprehension and meaningful involvement • Parental authority reigns if child dissents but sharing considered in their best interests even • Opt-out mechanism more practical		
	Feasibility (ws)		• Provide prospective counseling for critical care management is difficult for busy clinical teams • Some children may be unable to comprehend decisions, should be afforded extra protections	• Understanding data sharing benefits and risks is conceptually difficult for most children	
Parents should be informed in a transparent manner how their child's genomic and associated clinical data will be	Relative importance (SS)	• Relays confidence in technical systems • Prevents burdening parents with 'legalese'	• Its time and resource intensiveness may be more than research teams can manage • Stewardship becomes a bigger issue the longer		

securely managed and used.			data are kept		
	Confidence (ws)		• Powers that control systems and testing should be blocked • Should be contextualized with other statements e.g. respect for family ethnocultural backgrounds • Acceptability of data sharing activities should be judged according to original consent • Consent alone is insufficient, parents also require knowledge about procedure		
In a research context, data sharing infrastructures should enable children to withdraw consent to continued sharing of their genomic and associated clinical data when possible upon reaching the age of majority.	Desirability (ws)		• The relevance and time sensitivity of data when collected is a challenge, especially if longitudinal follow up is indicated		
	Feasibility (wo)			• Relies on a robust tracking system • Requires specific consent • uncertain if recontact threatens confidentiality • Implementation opportunities limited with database access terms • Logistical barriers	

Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance.	Relative importance (SS-ws)	• Clinical practice experience confirms this • Key to engagement with parents • Ideal for enabling future research • Central to the risk-benefit calculus of the decision		• It makes consent denser if imposed • Specific consent should always be required • Applies only to databases with limited access	
	Desirability (SS-ws)	• All involved should know the desired best practices & ensure these are upheld • Future data use is facilitated • Parents are engaged	• Will have a neutral effect • Broad consent to future use is better		• Parental authorization for future use and governance will have a harmful effect if targeted specifically to parents and not publicly accessible
Values conveyed by family, legal guardians or primary care givers should be respected when possible.	Relative Importance (SS-ws)	• It is central to the consent process	• There is no menu of data sharing options; either yes or no • There is natural attrition, those that share data are in research projects		• Families should not authorize future sharing at all if it conflicts with their values
	Feasibility (--)	• The consent process is meaningless without this respect	• Need to maintain relationships and revisit findings	• Communication is difficult, particularly when there is parent-child conflict	• Values are too cumbersome to track

				• Values are dynamic • Data sharing is all or nothing	accurately
All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent.	Desirability (SS-ws)	• Consent should be ongoing • This is standard practice • It is responsible conduct of research	• Balancing benefits and risks with parents may be beneficial insofar as it supports consent		• Mandating this may overwhelm professionals
	Feasibility (--)	• This is done routinely	• Ongoing clinical assessment presents challenges • Training and resources required to establish data privacy/safety infrastructures • Context dependent	• Consent procedures are suboptimal due to time constraints • 'All' professionals will be difficult to operationalize • Responsibility only rests with person obtaining consent	• Researchers may have no relationships to study participants
The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits.	Feasibility (SS-ws)	• Hypothetical risk conveyance needs to change • It is uncontroversial • It is standard practice for an ethics board	• Obtaining stakeholder buy in • Putting this evaluation into perspective for families		
	Confidence (SS-ws)	• Changes to risk communication are needed towards more evidence-based • Information dissemination is key	• Reliable but not sufficient for a robust data sharing framework; should be combined with meaningful informed consent		
Duplicative collection of genomic research data involving pediatric patients should be avoided.	Desirability (SS-ws)	• Clinical practice experience confirms families' strong desire for this • Repeat testing is	• Repeat data contribution does not result in added appreciable harm • it also avoids duplicating		• Avoiding duplicative data collection can be harmful

		wasteful • Leads to positive benefits but challenging for ongoing complementary studies	risks • re-identifying participants may post greater harm than duplication • conveys respect for participants • minimizes burden		because it places too much power in too few hands
	Feasibility (ws)		• reorganizing current practice • institutional coordination • resource constraints • unique identifiers complicate implementation for studies that recruit the same patients	• Difficulty related to dividing responsibilities between industry, research and testing centers • Reluctance to share data ownership • Trade-offs in confidentiality risk	• Reluctance to share data resources
Anonymized pediatric data should be made available via publicly accessible databases.	Desirability (SS-ws)	• Enhances knowledge	• Successes demonstrated in ultrarare disorders	• Risks outweigh the benefits for children	• Availability of data should only be linked to specific purposes; Facebook data breach is a cautionary warning
	Feasibility (--)	• Requires the least amount of oversight	• Jurisdictional differences in data protection • Consent requirements	• Uncertain governance framework • Mechanisms to update and interpret new data for clinical purposes	

Identifiable pediatric data should be made available using a controlled or registered access process	Desirability (SS)	• a needed improvement to current models • addresses bottlenecks to access	• Anonymized, not identifiable pediatric data should be made available using a controlled access process	• This data could be potentially re-identifying when combined with other databases and in ways that we may not appreciate at this time • Ethics boards may not be equipped to assess informational risks	
	Feasibility (SS-ws)	• Ethics boards already review data access processes	• Resources for clinical follow up, data governance and security infrastructures are simultaneously necessary • propriety datasets present competing interests • Cross provincial data consent/transfer must be sustainable		
Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.	Desirability (SS-ws)	• It incentivizes parents and families to 'donate' data • Providing opportunities does not obligate them	• Support is provided for clinicians to do this work • Clinicians can exercise professional judgment	• Sharing obligations may limit smaller, less complex projects • The obligation is to the patient, not to process	• Children and parents have no such obligations
	Feasibility (--)	• No hindrance to implementation	• Requires resources	• Additional resources are required • Explaining genetic analysis to lay people during consent processes is onerous & time consuming	

Table 14. Policy position statements ranked based on combined average of ratings across two categories following Round 1[xxiii]

#	POLICY POSITION STATEMENT	COMBINED AVERAGE RATINGS	RANK
8	The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits (F+C)	1.5	1
5	Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance (RI + D)	1.65	2
3	Parents should be informed in a transparent manner how their child's genomic and associated clinical data will be securely managed and used (RI + C)		
1	The best interest of children are primary (RI + F)	1.7	3
11	Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process (D +F)		
9	Duplicative collection of genomic research data involving pediatric patients should be avoided (D+F)	1.95	4
10	Anonymized pediatric data should be made available via publicly accessible databases (D + F)	2	5
7	All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent (D + F)	2.1	6
2	Children should be listened to, and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways (D + F)	2.15	7
6	Values conveyed by family, legal guardians or primary care givers should be respected when possible (RI + F)		
12	Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data (D + F)		
4	In a research context, data sharing infrastructures should enable children to withdraw consent to continued sharing of their genomic and associated clinical data when possible upon reaching the age of majority (D + F)	2.2	8

Round 2

Evaluating the underlying reasons

Twelve panelists participated in Round 2 (response rate 30%), in which they were requested to re-rate Statements 5-7 and 10-12. Panelists were provided a comprehensive summary of all Round 1 results prior to completing the Round 2 Delphi survey using the project website

[xxiii] RI = relative importance, **F** = feasibility, **C** = confidence, **D** = desirability

(www.projectpedigree.org). Each returning panelist reviewed their original rating, the group average and all qualitative feedback in response to Statements 5-7 and 10-12 retained after Round 1. Three new participants joined the panel, and were similarly provided group averages and anonymized qualitative feedback of panelists who participated during Round 1 (**Appendix B**). The amendment to Statement 7 and addition of Statement 13 to the overall KIDS framework were adopted based on a simple majority. While the amendments to Statements 10, 11 and 12 were narrowly approved numerically, content analyses of their corresponding qualitative rationales indicated they did not yield conclusive majorities.

A composite summary of all ratings from Round 2 is presented in **Table 15.** Statements 5-7 reached consensus statistically and qualitatively according to the evaluative thresholds applied during Round 1. Consensus and qualitative feedback for the newly proposed Statement 13 are provided in **Table 16**.

An inter-round comparison of the degree (**Table 17**) and direction (**Table 18**) of change in ratings for Statements 5-7 was conducted using data from 9 panelists who participated in both Rounds 1 and 2. Ratings decreased 2.2 points on average for Statements 5-7 after Round 2, suggesting an increase in perceived relative importance, feasibility and desirability. It is presumed panelists amended their original ratings and rationales after reviewing the composite results from the larger panel group. While the inter-round comparison for Statements 10-12 also indicated an overall negative direction of change (1.8 points lower), they yielded strong polarity and no consensus based on the modified de Loe's thresholds used in Round 1. Interquartile deviations were also calculated for each of the 6 statements re-assessed in Round 2 as a supplementary measure of consensus. Both calculations supported the conclusion that Statements 5-7 reached consensus after Round 2, while Statements 10-12 were retained for further analysis in Round 3 for low consensus and moderate-high polarity. Content analysis of panelists' rationales for the 4 amendments and 1 new policy position unveiled several key findings that are elaborated in detail below.

Exploring and obtaining the reasons for disagreements

The amendment to Statement 7 was approved with the largest majority (75%). Panelists reasoned that a trained delegate familiar with the anticipated benefits and risks of data sharing should be specified in Statement 7, as such individuals were perceived to be essential for facilitating an ethically robust consent process. One panelist suggested that a genetic counselor, specifically, should take the lead in this regard. Panelists who opposed the amendment cited ambiguity in necessary skillsets and

professional training of the 'trained designate,' as well as the scope of the designate's relationship with oversight bodies such as ethics committees and clinicians.

Two panelists argued that anyone entrusted with the informed consent task should be able to articulate the risk-benefit calculus for prospective data sharers, and be able to field any and all questions:

> The individual with the greatest content knowledge should be available to explain and answer questions–P8OYZ

> The PI is responsible for balancing risks and benefits related to the data sharing specified in their project, and the REB should be assessing this balance, but this is all done well before the actual time of obtaining consent. The balance should be explained in the ICF. Whomever obtains consent from the participant/family, eg. RA, coordinator etc, must however be able to sufficiently answer any questions they might have and be well enough informed to understand themselves the risks and benefits of data sharing. –Pa7KH

Eight panelists (67%) supported the decision to adopt Statement 13 related to the return of clinically actionable and validated genomic results, where its desirability and feasibility hinged on applying standard criteria for clinical actionability/validity e.g. American College of Medical Geneticists (Green et al. 2013) and identifying those responsible for clinical follow up and management in light of findings that meet these criteria. Several panelists interpreted the Statement to include the right *not* to receive results when not clinically actionable.

Both statistical and content analysis of voting results for amendments to Statements 10-12 yielded mixed results. Panelists were split on the decision to eliminate Statement 10 due mostly to discrepant views on anonymization fidelity. Reasons for eliminating the Statement related to children's vulnerability, the perceived myth of anonymization, uncertainty in the associated informational risks and ill-equipped governance structures to keep children's anonymized data secure.

Table 15. Summary results from Round 2 ratings of 6 policy position statements retained after Round 1. Policy position statements in grey were retained for re-assessment in Round 3.

#	POLICY POSITION STATEMENT	MEASURE	RATING 1	2	3	4	AVERAGE	CONSENSUS	SUPPORT	POLARITY
5	Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance.	Relative Importance	7	4	1	0	1.5	High	SS	None (0.45)
		Desirability	8	4	0	0	1.33	High	SS	None (0.24)
6	Values conveyed by family, legal guardians or primary care givers should be respected when possible.	Relative Importance	5	7	0	0	1.58	High	ws	None (0.27)
		Feasibility	1	4	7	0	2.5	High	wo	None (0.45)
7	All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent.	Desirability	7	4	1	0	1.5	High	SS	None (0.45)
		Feasibility	3	6	2	1	2.08	Mod	ws	None (0.81)
10	Anonymized pediatric data should be made available via publicly accessible databases.	Desirability	5	2	3	2	2.17	Low	SS-ws	Strong (1.42)
		Feasibility	5	3	4	0	1.92	Mod	SS-ws	None (0.81)
11	Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process.	Desirability	8	1	1	2	1.75	Mod	SS	Strong (1.48)
		Feasibility	4	5	2	1	2	Mod	SS-ws	Weak (0.91)
12	Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.	Desirability	8	1	2	1	1.67	Mod	SS	Strong (1.15)
		Feasibility	3	2	5	2	2.5	Low	--	Strong (1.18)

Table 16. Ratings and rationales for Statement 13.

	POLICY POSITION STATEMENT	MEASURE	RATING 1	2	3	4	AVERAGE	CONSENSUS	SUPPORT	POLARITY
13	Incidental (secondary) findings of clinically actionable genomic results should be made available	Desirability	6	4	2	0	1.66	High	SS-ws	None (0.45)
		Feasibility	0	9	2	1	2.33	High	ws	None (0.7)

REASONS FOR STRONG SUPPORT	REASONS FOR WEAK SUPPORT	REASONS FOR WEAK OPPOSITION	REASONS FOR STRONG OPPOSITION
• There is a duty to return these results • Withholding clinically actionable information is wrong • Consent to receive findings should be sought and respect for refusal honored • Meets the best interests standard	• It is clear to whom these results are made available • There is a shared criterion on clinical actionability re genomic results • Appropriate consultation and interpretation of results with families	• Accompanied by a duty to hunt • Results disclose predictive, adult-onset genetic conditions • Consent must be obtained upfront, but discrepancies exists when returning to adults vs. other vulnerable populations e.g. children, incompetent adults	
	• Inability to re-contact patients • Need for specialists/ized health professionals e.g. medical geneticists and genetic counsellors • Lack of standardization for clinical actionability • Uncertainty in who funds testing • Researchers should not have a duty to hunt	• Managing the clinical implications of the results • Resources are insufficient to interpret findings and wait times long for genetic services • Imposing mandates without clinical solutions is concerning e.g. scenario of rare disease diagnosis and no availability of orphan drug	• the statement is unclear whether researchers will be held to a duty to hunt

Table 17. Inter-round comparison of the degrees of change in returning panelists' scores on statements 5-7 and 10-12.

Statement 5 Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance.	**Relative Importance**		**Change?**	**Direction of change**	**Desirability**		**Change?**	**Direction of change**
	Round 1 score	Round 2 score			Round 1 score	Round 2 score		
P0Ehe7	1	1			1	1		
PAw34	1	2	*	[+] 1	1	1		
P3ew9	3	1	*	[-] 2	4	2	*	[-] 2
P8OYZ	1	2	*	[+] 1	1	1		
P6xHr	1	2	*	[+] 1	2	2		
PQnd4	3	3			2	2		
PHJR6	2	2			2	1	*	[-] 1
Pa7KH	2	2			2	2		
PSbg4	1	1			1	1		
Total				**[+] 1**				**[-] 3**
Statement 6 Values conveyed by family, legal guardians or primary care givers should be respected when possible	**Relative Importance**		**Change?**	**Direction of change**	**Feasibility**		**Change?**	**Direction of change**
	Round 1 score	Round 2 score			Round 1 score	Round 2 score		
P0Ehe7	1	1			1	1		
PAw34	1	1			2	2		
P3ew9	3	2	*	[-] 1	3	2	*	[-] 1
P8OYZ	2	2			2	2		
P6xHr	1	1			3	3		
PQnd4	2	2			2	3		
PHJR6	1	1			4	3	*	[-] 1
Pa7KH	3	2	*	[-] 1	4	3	*	[-] 1
PSbg4	2	2			3	3		

Total				**[-] 2**				**[-] 3**
Statement 7 All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent	**Desirability**		**Change?**	**Direction of change**	**Feasibility**		**Change?**	**Direction of change**
	Round 1 score	Round 2 score			Round 1 score	Round 2 score		
P0Ehe7	1	1			2	2		
PAw34	1	1			2	2		
P3ew9	4	2	*	[-] 2	3	2	*	[-] 1
P8OYZ	1	1			3	1		
P6xHr	3	1	*	[-] 2	4	2	*	[-] 2
PQnd4	2	2			2	2		
PHJR6	2	3	*	[+] 1	4	4		
Pa7KH	2	2			2	2		
PSbg4	1	1			1	1		
Total				**[-] 3**				**[-] 3**
Statement 10 Anonymized pediatric data should be made available via publicly accessible databases	**Desirability**		**Change?**	**Direction of change**	**Feasibility**		**Change?**	**Direction of change**
	Round 1 score	Round 2 score			Round 1 score	Round 2 score		
P0Ehe7	3	3			1	1		
PAw34	2	2			3	3		
P3ew9	2	1	*	[-] 1	3	1	*	[-] 2
P8OYZ	3	3			3	3		
P6xHr	4	4			2	1	*	[-] 1
PQnd4	1	1			1	1		
PHJR6	1	1			2	2		
Pa7KH	2	2			2	2		
PSbg4	1	1			1	1		

Total				**[-] 1**				**[-] 3**
Statement 11 Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process	**Desirability**		**Change?**	**Direction of change**	**Feasibility**		**Change?**	**Direction of change**
	Round 1 score	Round 2 score			Round 1 score	Round 2 score		
P0Ehe7	3	2	*	[-] 1	2	1	*	[-] 1
PAw34	1	1			2	2		
P3ew9	1	1			2	1	*	[-] 1
P8OYZ	4	4			4	4		
P6xHr	1	1			1	2	*	[+] 1
PQnd4	1	1			1	1		
PHJR6	2	1	*	[-] 1	1	2	*	[+] 1
Pa7KH	1	1			1	2		
PSbg4	1	1			2	2		
Total				**[-] 2**				**0**
Statement 12 Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.	**Desirability**		**Change?**	**Direction of change**	**Feasibility**		**Change?**	**Direction of change**
	Round 1 score	Round 2 score			Round 1 score	Round 2 score		
P0Ehe7	2	2			3	3		
PAw34	2	1			2	2		
P3ew9	1	1			2	1	*	[-] 1
P8OYZ	4	3	*	[-] 1	4	3	*	[-] 1
P6xHr	3	1	*	[-] 2	3	3		
PQnd4	1	1			1	1		
PHJR6	2	1	*	[-] 1	3	4	*	[+] 1
Pa7KH	3	3			3	3		

PSbg4	1	1			1	1		
Total				**[-] 4**				**[-] 1**

Table 18. McNemar change tables measuring directions of change in n= 9 panelist ratings between Rounds 1 and 2 for Statements 5-7 and 10-12. Red boxes indicate the number of panelists with a positive degree of change from Round 1 to 2 (i.e. lowered perceived value based on new Likert rating) while yellow boxes indicate the number of panelists with a negative degree of change (i.e. higher perceived value based on new Likert rating).

Statement 5—Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance.

Relative importance

	R2[xxiv]				
R1	VI	SI	SU	VU	
VI	2	3			5
SI		2			2
SU	1		1		2
VU					0
	3	5	1	0	9

Desirability

	R2				
R1	VD	D	U	VU	
VD	4				4
D	1	3			4
U					0
VU		1			1
	5	4	0	0	9

Statement 6—Values conveyed by family, legal guardians or primary care givers should be respected when possible.

Relative importance

	R2				
R1	VI	SI	SU	VU	
VI	4				4
SI		3			3
SU		2			2
VU					0
	4	5	0	0	9

Feasibility

	R2				
R1	DF	PF	PNF	DNF	
DF	1				1
PF		2	1		3
PNF		1	2		3
DNF			2		2
	1	3	5	0	9

[xxiv] **R1** = Round 1; **R2**= Round 2; **V**[x] = Very [Important, Desirable, Feasible]; **S**[x] =Somewhat [Important, Feasible]; **D** = Desirable; **U** = Undesirable; P[x] = Possibly [Feasible, Not Feasible]; **D**[x] = Definitely [Feasible, Not Feasible].

Statement 7—All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent.

Desirability

R1 \ R2	VD	D	U	VU	
VD	4				4
D	1	2	1		4
U	1				1
VU					0
	6	2	1	0	9

Feasibility

R1 \ R2	DF	PF	PNF	DNF	
DF	1				1
PF		4			4
PNF	1	1			2
DNF		1		1	2
	2	6	0	1	9

Statement 10—Anonymized pediatric data should be made available via publicly accessible databases.

Desirability

R1 \ R2	VD	D	U	VU	
VD	3	2			5
D	1				1
U			2		1
VU				1	1
	4	2	2	1	9

Feasibility

R1 \ R2	DF	PF	PNF	DNF	
DF	3				3
PF	1	2			3
PNF	1		2		3
DNF					0
	5	2	2	0	9

Statement 11—Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process.

Desirability

R1 \ R2	VD	D	U	VU	
VD	6				6
D	1				1
U		1			1
VU				1	1
	7	1	0	1	9

Feasibility

R1 \ R2	DF	PF	PNF	DNF	
DF	1	3			4
PF	2	2			4
PNF					0
DNF				1	1
	3	5	0	1	9

Statement 12—Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.

Desirability

	R2				
R1	VD	D	U	VU	
VD	3				3
D	2	1			3
U	1		1		2
VU			1		1
	6	1	2	0	9

Feasibility

	R2				
R1	DF	PF	PNF	DNF	
DF	2				2
PF	1	1			2
PNF			3	1	4
DNF			1		1
	3	1	4	1	9

One panelist argued that children's consent-related vulnerability can be exacerbated where informational risks are unknown, and particularly if the then-adult's decisions about their data do not align with those their parents made on their behalf at the time of data contribution. Furthermore, "open [i.e. broad] consent is imperfect and thus should be restricted to adults" (POEhe). In contrast, one panelist's vote to preserve Statement 10 was premised on accepting equal degrees of risk for both adults and children: "I do not believe the risks to children in collecting and making available data (with protections considered adequate for adults) are unreasonable or that the level of risk alone would justify restricting its use… we permit use of anonymized data without consent (sometimes even without REB review) for adults. I don't think we can base this argument on level of risk (in the data sharing context) when we permit such practices for adults" (Pa7KH).

Invoking the same respect for persons principle that POEhe used to justify eliminating Statement 10, panelist PQnd4 justified its preservation on the basis that "Denying families the ability to help other children (and possibly their own child as well) by sharing genomic and associated clinical data is paternalistic and can be seen as violating their autonomy." This finding is striking in that two different interpretations of the same ethical-legal principles—respect for persons and protection of the child's future autonomy—were reflected in opposing positions on the permissibility of sharing anonymized data.

There was a particularly strong sense from two panelists that "true anonymization is a myth" (Pgw85), and that "it is likely not possible to anonymize data derived from genetic testing even with today's technology" (8OYZ). The ability to re-identify an individual using genomic data was considered a formidable risk irrespective of efforts to anonymize such data. Skepticism of whether true anonymization could be achieved heightened, in turn, the perceived levels of risk associated

with sharing: "[There is] not enough detail to support [sic] statement. Risks of re-identification are too great and data types are too variable to have a blanket statement" (8OYZ). The data sharing conservatism reflected in the above arguments was met with equal data sharing confidence. Panelists argued that the risks associated with sharing anonymized data were both minimal and uncontroversial, supporting the appropriateness of Statement 10 in the overall KIDS framework. One panelist argued the delinking procedures that anonymized data often undergoes effectively "protects individual confidentiality while putting valuable data in the public domain. Such data is good for the quality of aggregate data but not for individual medical care" (Pazbd). Given effective delinkage, "anonymized data is very low risk," and rather "the significant risk is related to lack of data sharing when it comes to children and slowing the field of research" (Psbg4).

Votes to amend Statement 11 were divided evenly according to the descriptive statistical analysis (**Table 19**). Analysis of panelists' qualitative feedback, however, lent an alternative perspective on why panelists were split in their overall support for Statement 11. Four panelists voted in favor of the amended Statement 11, 4 voted against and 5 disagreed with both the original and the amended statement. The primary source of tension in proposing to make identifiable data accessible only through a controlled access process centered on whether controlled access indeed affords the appropriate level of security for coded data i.e. data that retains personal identifiers. The most impassioned rationale for supporting the amendment was one that reminded stakeholders of the spirit in which clinicians and researchers make data involving children accessible in the first place: "Again this is about not overprotecting children and delaying research" (PSbg4).

Two dissenting panelists argued in favor of more stringent user authentication: "the best approach would be anonymized data made available through a controlled access process" (P0Ehe). In contrast, one panelist suggested registered access was an efficient and economically more viable option for accessing coded pediatric data insofar as it ensures "robustness of the applicant authentication process" (Pazbd). Yet another panelist emphasized it would be "important to know who is accessing data and why it is being accessed" (P6Hrq). Of those who disagreed with both the original and amended Statement 11, several panelists believed a statement outlining access regimes for identifiable data was inappropriate given "the risks have not been well enough established, and the statement is premature" (PgW85).

Table 19. Results of panel decisions on 4 amendments to policy positions statements suggested after Round 1

AMENDED STATEMENT	AGREE	DISAGREE	DECISION

Professionals involved in consent processes related to data sharing and data-intensive research have the responsibility to balance potential benefits and risks. A trained designate should be available to discuss these with parents at the time of consent.	9 (75%)	3 (25%)	Approved
Anonymized pediatric data should be made available via publicly accessible databases.	6 (50%)	6 (50%)	Undecided
Identifiable pediatric genomic and associated data should be coded and made available through a controlled access process.	6 (50%)	6 (50%)	Undecided
Providing children and their families the opportunity to share their genomic and associated data is an obligation of researchers.	5 (42%)	7 (58%)	Rejected
Incidental (secondary) findings of clinically actionable, validated genomic results should be made available.	8 (67%)	4 (33%)	Approved

Although the amendment to Statement 12—proposing an obligation to provide children and their families with opportunities to share their data should be restricted to researchers—failed by a narrow majority (58%). The vote, however, elicited contradictory rationales on its perceived burdens. **Table 20** summarizes these arguments and lends further insight into why the amendments to Statements 12 on data sharing obligations and access to anonymized versus coded data failed to reach consensus after Round 2. For example, several non-clinician panelists advocated to narrow this obligation because it "would be an undue burden on clinicians but makes eminent sense for researchers," and that "not all researchers have the means to achieve this. Data sharing is not appropriate for all types of genomic research" (PIcHg). A clinician panelist, by contrast, provided the following impassioned arguments opposing such a restriction, drawing on their own clinical experience to demonstrate the clinical merits of providing families with opportunities to share data using pediatric oncology as an exemplar case:

> Absolutely not!!!!! My clinical practice is consumed by doing genomic testing on patients, as is that of many of my pediatric specialty colleagues. Restricting data sharing to the narrow silo of researchers is going to miss vast amounts of highly valuable information, directly relevant to clinical practice. Be reminded of how childhood cancer has gone from a universally fatal disease to one with about 95% survival in a generation because of data sharing amongst clinicians. This data ranged from clinical presentation and outcomes to biomarkers and other basic science findings, but was utterly not restricted to that generated by researchers (PAw34)

Other panelists shared the above view that too narrowly restricting the obligation to provide opportunities to share data was not ideal, particularly as clinical sequencing is expected to increase, the role of researcher may be undefined, and that "data from the medical care context is equally important for better science" (PazbD). "This statement", as one panelist suggested, is also "directed at clinical labs, not just researchers (who increasingly recognize and are required by their funders to share genomic data)" (PQnd4). Despite emphasizing that this statement intended to obligate providing the *opportunity* to share, rather than obligating sharing per se, several panelists rejected this obligation in principle (Pa7KH) "even if highly desirable" (PHJR6). Despite considerable variability in panelists' views on whether and how the KIDS framework should operationalize this data sharing obligation, the desirability ratings for Statement 12 indicated the greatest degree of change for a single rating between Rounds 1 and 2[xxv]. Statement 7 achieved the greatest degree of change across both rating categories, desirability and feasibility, dropping 3 total Likert points between Rounds 1 and 2 (**Table 18**).

Re-evaluating the options

Statements 10, 11 and 12 were retained for further assessment in Round 3 for failing to achieve consensus after both re-rating and amendment exercises during Round 2. Qualitative feedback corroborated this lack of consensus, as well as the moderate- high degrees of polarity indicated. The content analysis revealed two additional key findings. First, rationales reflected conflicting relationships between mechanisms of data access and responsible oversight for two of the types of pediatric data raised in this thesis, *irretrievably delinked* i.e. anonymized data and *coded* data; second, that the desire to facilitate group consensus could have motivated some panelists' vote to approve amendments on statements perceived as particularly controversial, namely Statement 10 and 11 (**Table 19**).

[xxv] Overall desirability ratings for Statement 12 dropped 4 Likert points between Rounds 1 and 2, indicating a higher perceived value after reviewing group responses and rationales.

Table 20. Summary of content analysis results on reasons given for 3 policy positions statements ranked lowest in feasibility after Round 1.

Statement	Content analysis summary [No. panelists citing this reason]
Values conveyed by family, legal guardians or primary care givers should be respected when possible	• No barriers to feasibility beyond those associated with the general consent process [1] • Improve ability to assess family values [2] via --standardizing questionnaires [1] --tool development [1] • Differentiate values assessment in research and clinical contexts [1] • Include family/caregivers at the time of consent [1] • Allow data sharing choices that --are not conditional on research participation [1] --restrict future, unspecified uses of data [1] --mandate re-consent for each use [1] • Improve bidirectional communication [1]
All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent	• Basic requirement as per ethics principles related to --informed consent [2] --responsible conduct of research [1] • Ensure standards for consent process via --verifying the process is commensurate with levels of risk the data sharing poses [1] --improving accessibility of consent language [1] • Barriers to feasibility are technical aspects of data security and quality which prevent realistic understandings of risks and benefits within the research enterprise [1] • Feasibility of balancing unrealistic risks after consent due to other clinician demands [1] • Limit the obligation to some, but not all health professionals because --of an inability to discuss potential benefits risks or consent families [1] --infrequent or indirect contact with families [3] --the obligation is too extensive [1] • Enhance researcher education/knowledge on data sharing benefits and risks [2]

Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data	• Improve data infrastructures and ensure adequate resources to support them [3] → multicenter databases and information sharing platforms [2] • Feasibility strengthened by a rights-based principle that supports the statement [1] • Specify types of sharing that can be expected e.g. return of material findings [1] • There is no such obligation [1] • Additional human and material resources needed [1]

Finally, results from Round 2 indicated polarizing disagreement on who ultimately bears data management, protection and clinical interpretation responsibilities for children's genomic and associated clinical data. This finding was especially evident in exploring whether an obligation to provide the opportunity to share data should be restricted to researchers considered in the amendment to Statement 12. It was also discussed in the context of standardizing criteria for clinical actionability for returning validated incidental findings as implicated in Statement 13 (**Table 16**). The conceptual themes linking data access/security, governance and the scope of clinical benefit together comprised the foci for re-assessments conducted in Round 3.

Round 3

Round 3 enabled in depth exploration of the relationship between the data access and ethics governance themes described above. It also sought to confirm upon whom data management and security responsibilities should rest in Canada from the perspective of Canadian pediatric genomic data sharing stakeholders.

Eleven complete surveys were analyzed in Round 3[xxv] (response rate 26%), in which panelists considered the relationship between data access and requisite oversight/governance for sharing both anonymized and coded genomic data involving children. Prior to completing the Round 3 survey, panelists were directed to the project website for a comprehensive summary of all Round 2 results (**Appendix B**). The summary results page detailed group averages as well as all qualitative feedback provided in response to Statements 5-7 and 10-12. The summary page also presented results of the 1 approved, 1 failed 2 undecided amendments Round 2 assessed (**Table 19**), and notified panelists of the formal decision to adopt Statement 13 based on voter responses.

Exploring and obtaining the reasons for disagreements

Two thirds of panelists (67%) reported that controlled access was the most appropriate mechanism for sharing anonymized i.e. irretrievably delinked data. One third of panelists named research ethics committees as those entities lending the most appropriate oversight for accessing such data (**Figure 4**). Panelists agreed that controlled access was also the most appropriate mechanism for coded data (91%), and research ethics (36%) and data access committees (36%) were equally suggested as lending the most appropriate oversight for sharing this data (**Figure 5).** When asked to indicate all

[xxv] Partial data collected from one panelist during Round 3.

the data sharing stakeholders who should be responsible for consenting children and their families for the opportunity to share their genomic and associated clinical data, panelists chose principal investigators most frequently (9 votes) closely followed by clinicians (6 votes) (**Figure 6**). This finding was consistent across all data sharing stakeholders reflected in the Delphi panel.

Figure 4. Results from 10 panelists in Round 3 in response to *Which of the following lend the most appropriate oversight for responsible sharing of irretrievably delinked i.e. anonymized genomic data involving children?*

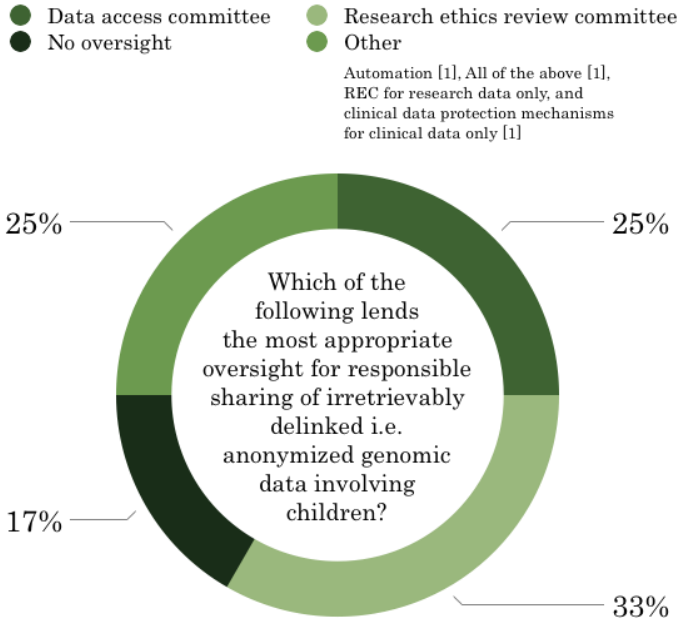


Figure 5. Results from 10 panelists in Round 3 in response to *What is the most desirable mechanism of access to anonymized genomic data involving children?*

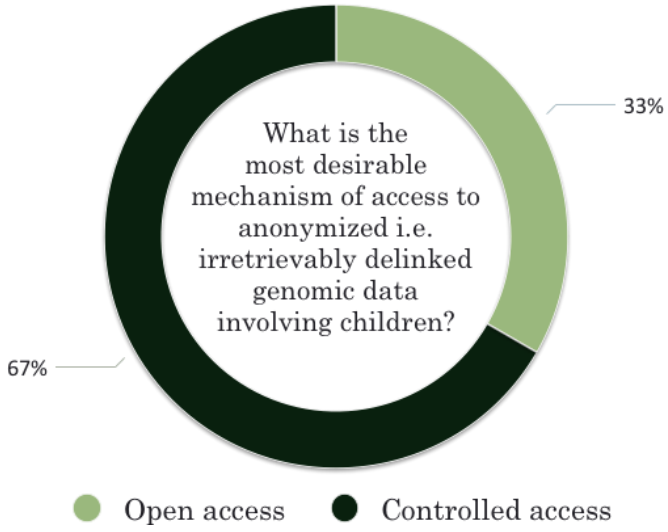


Figure 6. Results from 10 panelists in Round 3 in response to *Which of the following lend the most appropriate oversight for responsible sharing of coded genomic and associated clinical data involving children?*

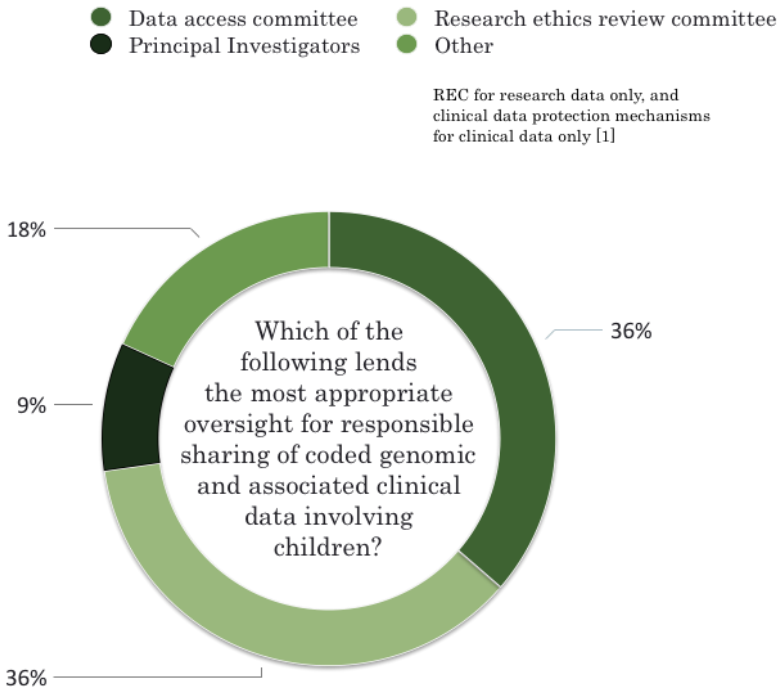
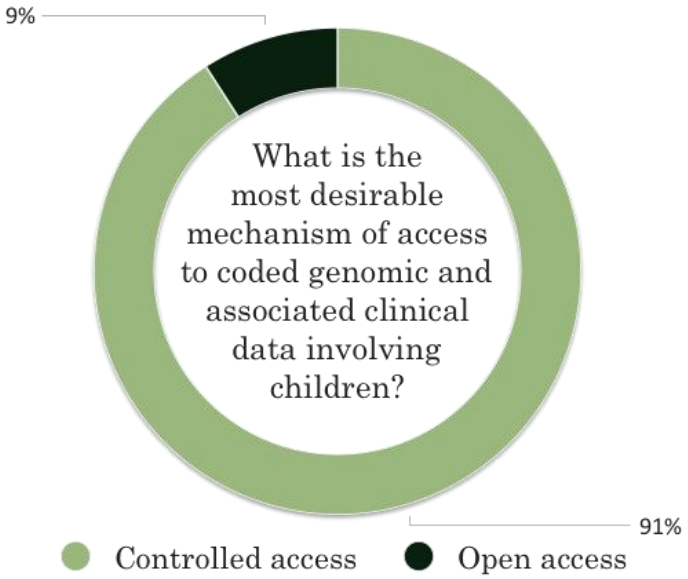


Figure 7. Results from 10 panelists in Round 3 in response to *What is the most desirable mechanism of access to coded genomic data involving children?*



Evaluating the underlying reasons

That no panelist suggested barring all access to anonymized or coded data (**Figure 7**) corroborates findings from the systematic review of reasons that underpinned the initial KIDS framework. The primary justification for panelists' overall preference towards controlled access for anonymized genomic data (67%) followed from the idea that true data anonymization is questionable at best, and risky at worst. Importantly, the reasons informing panelists' skepticism differed. Panelist P80YZ argued, for example, "Technology is rapidly evolving, and one can imagine, in the near future, that it will not be possible to guarantee anonymity, particularly where genetic data are concerned." Other panelists, in contrast, agreed that genomic databases are currently facing the future P80YZ envisaged where true anonymization is impossible:

> The concept of irrevocable anonymization needs to be recognized as a mythology--the genomic data itself contains the means to identify individuals. As such, free and open access put children at risk–PgWH5
>
> I think there should be access but controlled given the possibility of re-identification - in this era of technology, likely possible even with apparently delinked data—PHJR6
>
> It shouldn't be available openly, since large genomic datasets may be identifiable despite de-identification—PIcHG

Three panelists unequivocally supported open access to anonymized pediatric data and were guided by a strong conviction in the fidelity of current anonymization standards aimed at keeping children's personal identifiers secure. **Table 21** presents a summary analysis of their reasons.

Table 21. Summary of content analysis on reasons given for the most desirable mechanism of access to anonymized genomic data involving children? [No. panelists]

	Open Access	**Controlled access via user authentication**
Anonymized		
	• Identifiable links are irretrievable & sometimes unnecessary [2] • Minimal risk [3] • Making anonymized data openly available is ensuring quality of care & improvement [1]	• Benefits of data availability outweigh harms [1] • Free & open access puts children at risk [3] • True anonymity is not

	• Facilitate clinical collaboration necessary to interpret VUS [1]	guaranteed [5]

Indeed, making coded data publicly available was considered a norm for quality care delivery and improvement despite the higher risk of re-identification that sharing can pose for children with rare genetic disease, in specific, relative to depositing genomic data into a general variant database. Sharing coded data as a general practice of clinical care was particularly salient for interpreting variants of unknown significance (VUS), as one panelist described. Based on the rationale below, and others analyzed during Round 3, it was determined that associated informational risks for sharing anonymized data, albeit minimal, were largely determined by the i) the number of reported cases or variants available in a database and the ii) provenance of the data i.e. where the data was sourced according to panelists who opted towards open access:

> If you have tons of children and just list of variants, and maybe one additional source of data, then yes you may have more likelihood of knowing who that patient is. But this does not matter in the long-term if you ask patients and their families especially in the rare disease context; The collection source matters more when it comes to consent; if clinical data is coming from an institution, where a patient has not consented you should definitely hold this data to the highest possible risk and threat—PSbg4

Furthermore, the analysis of qualitative rationales for preferred access regimes to coded data yielded two observable patterns in argumentation between anonymization-skeptics and supporters as illustrated in **Table 22**.

Table 22. Summary of content analysis on reasons given for the most desirable mechanism of access to coded genomic and associated clinical data involving children? [No. panelists]

	Open Access	**Controlled access via user authentication**
Coded		
	• Preserving an identifiable link allows revision & updating of clinical information with direct clinical utility [1]	• Balancing harm of sharing with harm of NOT sharing [1] • Higher risk [3] • Greater control is warranted when able to link back to patient [4]

One pattern was observed in the ways in which panelists described the roles of future and current data infrastructures. The technological evolution witnessed in the data intensive sciences, and the emerging data ecosystems it is enabling, were capitulated among anonymization-skeptics in the Delphi panel as verifiable reasons to sound caution on genomic data sharing writ large. Panelists who trusted in the anonymization process—as inferred from their positive position on open access regimes—instead offered case examples of how systems innovations made possible new clinical discoveries with direct clinical implications in areas such as rare genetic disease:

> The clinical world is moving ahead in leaps and bounds. Just last week we met with one of the large genomic diagnostic services (Blueprint Genetics). They have instituted a system whereby clinicians can provide updated info about their patients who have been determined to have a variant of unknown significance (VUS; a big finding these days), and BG will then internally assess if the new info about a specific patient affects the VUS interpretation, and if so, they will update their site and provide an updated report to any other clinicians/patients who have had this same finding. AND, the Clinical Immunology Society (USA) just today announced that they have established a registry where clinicians can post phenotype and genotype info about patients found to have VUS, in order to improve interpretation of VUS and facilitate connections between clinicians who want to study similar cases. In both these examples, patient identifie[r]s are completely unnecessary - it is the nature of the genetic info and associated clinical info that is key.—PAw34

When prompted about the most appropriate level of oversight for coded data, panelists overwhelmingly supported controlled access regimes (**Table 23**). Data that enables "identifiable links to children and their clinical data" (PIcHG) warrant greater access controls according to n= 9 panelists (91%) because such linkage poses higher informational risks. For one panelist, however, open access to coded patient level data was justifiable on the account that this practice was commonplace in some clinical arenas, and offered anecdotal support for their position:

> I was contacted a short while ago by another clinician who discovered we had a patient with the same mutation as one he had, through publication of my associate's PhD thesis which researched this case. And, when a new biologic targeting specific mutations in Cystic Fibrosis, every parent in BC with a CF child knew about the 2 siblings in the province with that mutation (family blogs, community connections, media etc)—PAw34

Table 23. Summary of content analysis on reasons given for the most appropriate oversight of both anonymized and coded genomic data involving children (No. panelists)

	REC (N= 4)	**DAC (N= 3)**	**PI (N = 0)**	**No oversight (N=3)**	**Other (N = 3)**
Anonymized					
	• Continued review & oversight are required because true anonymization is not guaranteed [4] • Only means of providing protections because of PI & clinical potential conflicts of interest [2] • Data access committees will vary in degree of oversight, & are not subject to RECs rules [1]	• Research ethics committees make access highly inefficient [1]			• Automate publicly available access with authorization process to monitor uploads and permissions [1] • REB for research data; existing medical record protection schemes for clinical data [1] • All listed stakeholders need to be involved to promote efficiency & proportionality [1]
	REC	**DAC**	**PI**	**Other**	**Other**
Coded					
	• REC is most at arms length from patient and investigator; minimizes conflict of interest [2]		• Only the PIs would have the capacity to oversee data sharing but are not always best positioned to protect the rights and well-being of participants [1]	• REB for research data; existing medical record protection schemes for clinical data [1]	• REB for research data; existing medical record protection schemes for clinical data [1]

To clarify the polarization and low consensus for Statement 12 regarding potential professional duties, Round 3 prompted panelists to name those professionals who would be best served to discuss data sharing opportunities and consent families. In addition, panelists were asked to identify infrastructural resources and support needed to facilitate the abovementioned professionals in their duty to discuss data sharing opportunities. **Figure 8** summarizes the results of the former by profession, where panelists overwhelmingly named principal investigators (N=9 panelists), followed by clinicians (N =6) as the most appropriate professionals to serve in this role. While several panelists agreed principal investigators were responsible for ensuring consent was obtained according to regulatory norms and cultures of practice, the therapeutic relationship fostered between clinicians and families made clinicians ideal for engaging families in the actual consent process. Genetic counselors were also named as important facilitators for data sharing discussions (N=3) insofar as they were properly trained by research/clinical ethicists to contextualize the linkage implications of sharing associated clinical data for research purposes, for example.

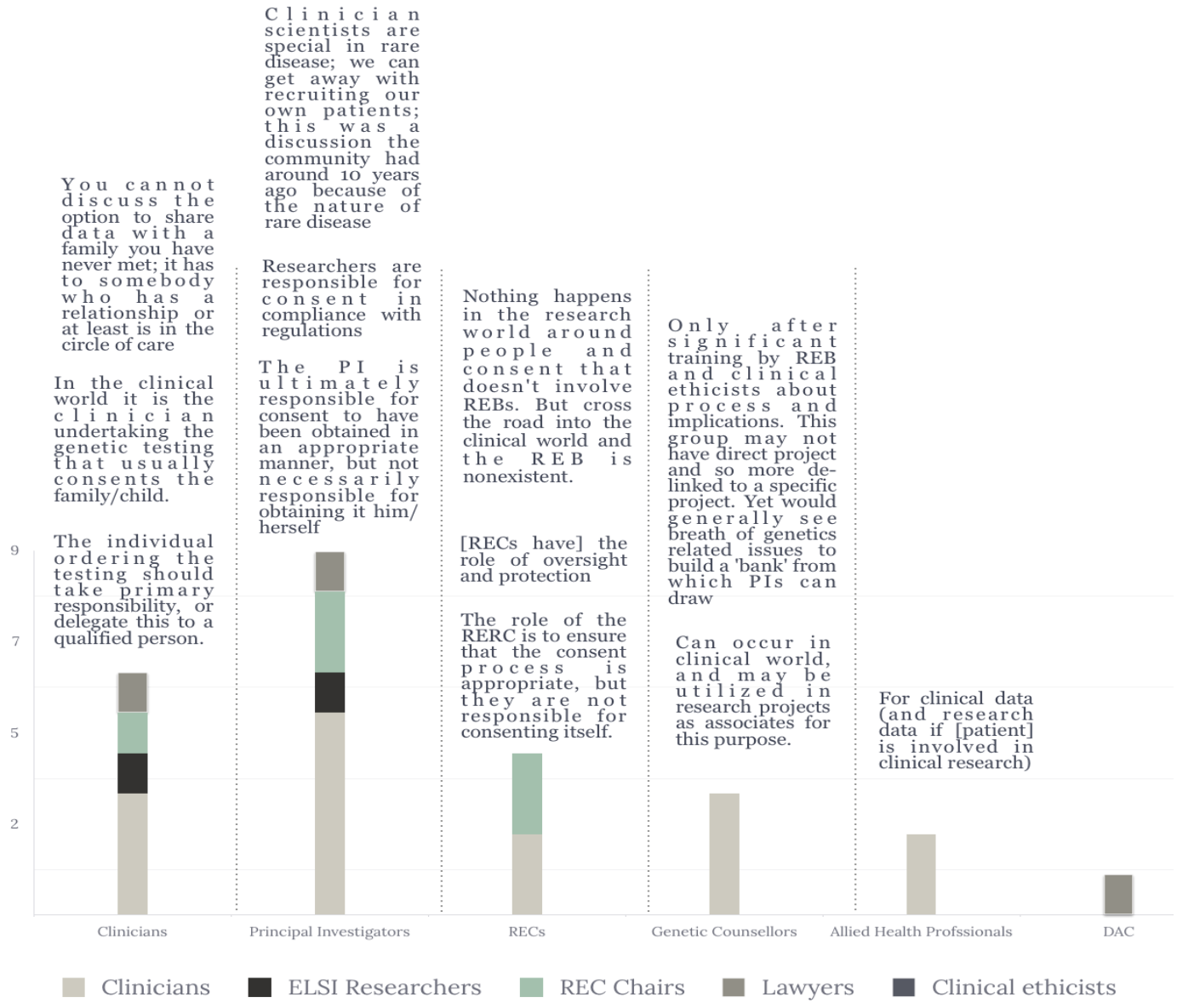
Panelists argued that a combination of technological, material and human resources were needed to fulfill the professional obligations outlined in Statement 12. **Table 24** categorizes these sources into 6 main themes. Electronic consents and shared information platforms/database infrastructures were the most frequently cited technological resources.

Table 24. Technological, material and human resource supports needed to discuss data sharing opportunities with children and families.

Technological	**Material**	**Human**
Electronic consent	Salary support/funding	Training --study benefits & risks --enhance REC expertise
IT infrastructure --information sharing --data access and security	Time --consent families	Consenting personnel

Three panelists argued that database support for IT infrastructures was specifically important for ensuring adequate data access oversight and security, while 1 panelist promoted shared data platforms that "clinicians, families and researchers can contribute to and benefit from" (P3ew9). Salary support/funding (N=2 panelists) and time (N=4) were among the most important material resources panelists cited to meaningfully consent patients and families, particularly for busy clinicians and research coordinators. Lack of adequate training and availability of allied health professionals were together put forth as major human resource gaps that would be required to explain relevant risks and benefits of data sharing (N=4): "I think someone in the research team needs to be trained to explain this data sharing opportunity to children and their families, and to go through the consent process with them. This could be a research genetic counselor, a research nurse, or other appropriately trained team member" (PIcHG). Moreover, 2 panelists specified that research ethics committees had relevant training responsibilities in this regard.

Figure 8. Descriptive statistics and qualitative results from 10 panelists in Round 3 in response to *Who is responsible for consenting children and their families about the opportunity to give their permission to share genomic and associated clinical data? Check all that apply and briefly describe the role they play in the consent process.*



Re-evaluating the options

Irreconcilable positions on the fidelity of de-identification techniques and the perceived informational risks they posed—both normative foundations upon which consensus for Statements 10 and 11 relied—informed the decision to close the policy Delphi after Round 3. Two dissenting positions emerged in the qualitative data when analyzed with attention to how panelists constructed 'responsible' sharing of anonymized versus coded genomic data. Qualitative content analysis revealed the primary source of their dissent was whether true anonymization of children's genomic data could be achieved given the current state of emerging computational capacities driving the data-

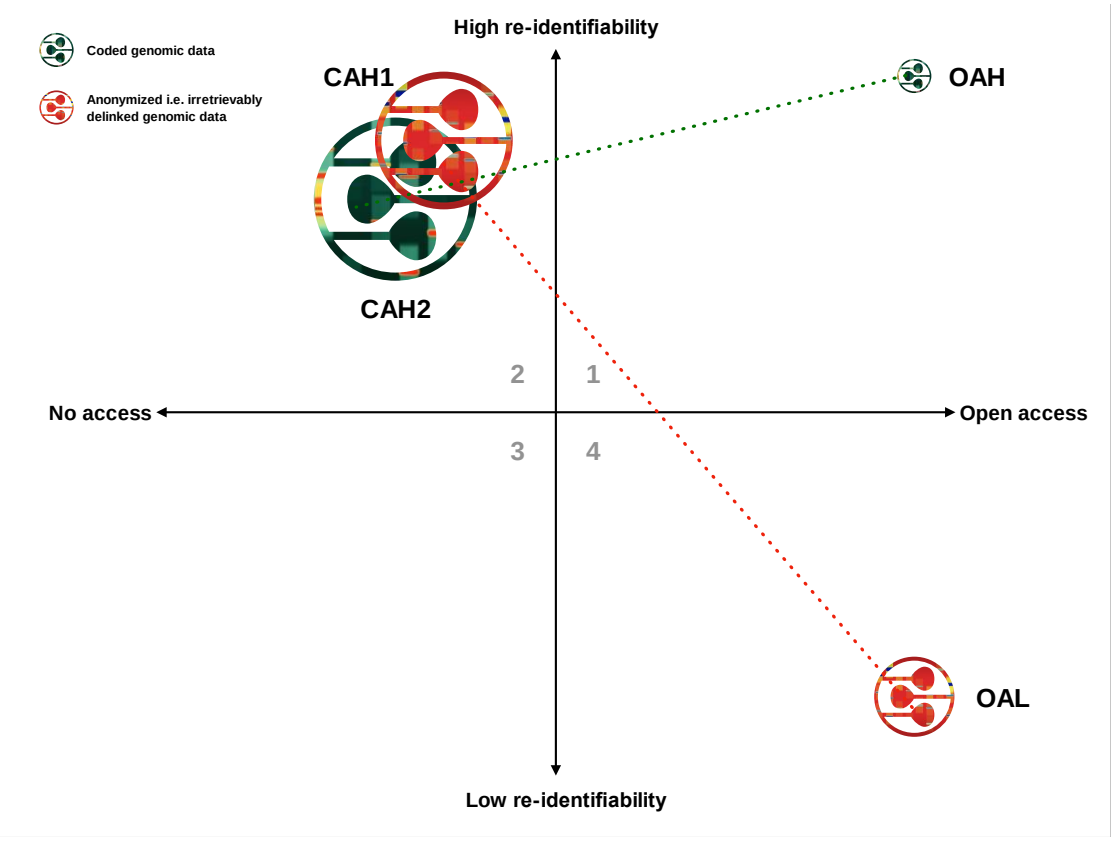
intensive sciences. This general skepticism concerning anonymized data—as well as the actual process of anonymization—motivated many data sharing stakeholders in this study to advocate for stricter data access arrangements than those sanctioned under applicable clinical or research data protection regulations. These results may have differed if panelists were asked to qualify the differences between patients who shared data as part of clinical research related directly to their care, or those who participated in biomedical research generally.

Round 3 therefore sought to nuance the three policy-relevant themes that guided Statements 10, 11 and 12: data type e.g. anonymized versus coded, perceived informational risks of sharing and the appropriate data access regime. Qualitative data collected across Rounds 1-3 suggested panelists appeal to three interrelated considerations in how they perceive responsible governance of pediatric data sharing: i) security in the data's source, ii) oversight of its proposed uses and iii) access controls commensurate with the data's overall degree of sensitivity. **Figure 9** maps these relationships onto a quadrant matrix, where data access regime and perceived likelihood of re-identification are situated on the two axes for comparison.

Four access-identifiability relationships were identified based on qualitative and descriptive statistic data collected during Round 3. The sizes of the circles in **Figure 9** correspond to the degree of support for their position in the quadrant based on data type—anonymized genomic data in red, coded data in green—and where the distance between two circles of the same color is understood as the strength of dissent analyzed in panelists' qualitative responses.

The first typology identified, OAH, is reflected in quadrant 1. OAH corresponds to data with high perceived likelihood of re-identifiability with an open access regime. One panelist articulated this relationship with respect to access to coded genomic and associated clinical data, in which "Preserving an identifiable link allows revision and updating of clinical information which could range from evolving phenotype, other affected sibs in a family, through to responses to therapies (especially targeted precision biologics for, say, gain-of-function mutations. Again, the horse has left the barn in the clinical arena on this matter." Indeed, the high likelihood of re-identifiability may be a necessary feature of good clinical care when it enables clinicians to go back to the patient when new clinical care knowledge evolves via reclassification of a previous VUS, for example. All other panelists agreed that coding children's genomic and associated clinical data inherently increases the likelihood of re-identifiability—often purposefully for the aforementioned reason—but advocated unanimously for controlled data access via user authentication. CAH2 reflects this relationship.

Figure 9. Decision-making typologies compared by data access regime and perceived likelihood of re-identifiability based on mixed methods analysis of Round 3 data.



Two access-identifiability relationships, CAH1 and CAH2, map onto quadrant 2, wherein panelists reasoned that both anonymized i.e. irretrievably delinked as well as coded genomic data confer a high likelihood of re-identifiability and, as such, warrant access controls. No panelist advocated for barring access to either coded or anonymized genomic data where this data confers a low likelihood of re-identifiability, hence no access-identifiability relationship was observed in quadrant 3. OAL is the final typology modeled from Round 3 data, and reflects the view that anonymized genomic data poses "super minimal risks" (PSbg4) and therefore "No oversight is required because it is irretrievable; people cannot be identified anyways" (PSbg4).

Decisions informing preferred access regimes for both anonymized and coded data coincided with perceived informational risks some panelists associated with the respective data type. Discrepant views on the fidelity with which panelists believed patients and their families could be re-identified from sharing anonymized genomic data explains the strength of the dissent between

typologies CAH1 and OAL. The majority of clinician-scientists, for example, implicitly differentiated this likelihood when advocating for open access regimes to anonymized data. Research ethics committee (REC) chairs, in contrast, made no such distinction, an observation corroborated in their advocacy for controlled access regimes irrespective of the data type i.e. anonymized and coded data. Re-identification was, in the views of REC chairs, equally likely for sharing anonymized or coded data and therefore only controlled access enabled responsible sharing.

Discussion and Conclusion

This policy Delphi resulted in consensus validation of 10 policy position statements regarding ethical-legal, social and scientific factors of pediatric data sharing (**Table 25**). Qualitative content analysis pointed to a triangulation of confidence in technical work, governance and public engagement that can together explain how Canadian stakeholders involved in this policy Delphi study construe responsible genomic and associated clinical data sharing involving children.

Table 25. Nine policy positions of the KIDS Framework prioritized among Canadian data sharing stakeholders based on statistical and qualitative results from a three-round policy Delphi Study

The best interests of children are primary
Children should be listened to, and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways
Parents should be informed in a transparent manner how their child's genomic and associated clinical data will be securely managed and used
In a research context, data sharing infrastructures should enable children to withdraw consent to continued sharing of their genomic and associated clinical data when possible upon reaching the age of majority.
The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits
Duplicative collection of genomic research data involving pediatric patients should be avoided.
Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance
Values conveyed by family, legal guardians or primary care givers should be respected when possible
All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent
Incidental (secondary) findings of clinically actionable genomic results should be made available

Statement 8— The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits—and Statement 5— Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance—ranked first in priority based on a combined statistical and qualitative

analysis across both their rating categories following Round 1 (**Table 26**). Assessing risks and benefits, and the informed disclosure of how data will be used at the time of collection and potentially in the future are all requisite elements of informed consent processes for research participation, generally. It is therefore unsurprising that Statements 5 and 8 were considered the highest prioritized statements among panelists in this study. Listening to children in developmentally appropriate ways (Statement 2) and enabling children to withdraw their data upon reaching the age of majority (Statement 4) achieved the lowest combined ratings yet reflected broad agreement on from the panel on their low priority status.

Table 26. Rankings list for policy position statements based on combined average ratings across two categories after Round 1 (n=10 panelists) and Round 2 (n =12 panelists)[xxvi]. Policy position statements in grey represent those not reaching consensus after Round 3.

	After Round 1		**After Round 2**	
	COMBINED AVERAGE	**RANK**	**COMBINED AVERAGE**	**RANK**
POLICY POSITION STATEMENT				
The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits (F+C)	1.5	1	1.5	2
Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance (RI + D)	1.65	2	1.41	1
Parents should be informed in a transparent manner how their child's genomic and associated clinical data will be securely managed and used (RI + C)	1.65	2	1.65	3
The best interest of children are primary (RI + F)	1.7	3	1.7	4
Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process (D +F)	1.7	3	2	7
Duplicative collection of genomic research data involving pediatric patients should be avoided (D+F)	1.95	4	2	7
Anonymized pediatric data should be made available via publicly accessible databases (D + F)	2	5	2.04	8
All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent (D + F)	2.1	6	1.79[xxvii]	5
Values conveyed by family, legal guardians or primary care givers should be respected when possible (RI + F)	2.15	7	2.04	8
Children should be listened to, and involved in decision-making processes related to genomic and associated clinical	2.15	7	2.15	9

[xxvi] **RI** = relative importance, **F** = feasibility, **C** = confidence, **D** = desirability

[xxvii] Statement amended in Round 2 to read: Professionals involved in consent processes related to data sharing and data-intensive research have the responsibility to balance potential benefits and risks. A trained designate should be available to discuss these with parents at the time of consent (D + F)

data sharing in developmentally appropriate ways (D + F)				
Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data (D + F)	2.15	7	1.88	6
In a research context, data sharing infrastructures should enable children to withdraw consent to continued sharing of their genomic and associated clinical data when possible upon reaching the age of majority (D + F)	2.15	8	2.15	9
Incidental (secondary) findings of clinically actionable, validated genomic results should be made available	_	_	2	7

The logistical challenges of data withdrawal, and an inability to provide diverse data sharing options in accordance with family values could underscore why these statements ranked lowest relative to other statements in the KIDS framework. Indeed, these results and potential explanations corroborate those from the systematic review of reasons.

Statements 10, 11 and 12 consistently ranked among the lowest rated position statements despite wide support in the literature for open and controlled regimes of access for anonymized and coded genomic data, respectively. All three statements failed to reach consensus, and were thus not validated for application in the Canadian pediatric data sharing context . In response to failed consensus on these statements after Round 2, Round 3 sought to qualify the normative relationships between risk, oversight and access that underpinned panelists' dissent. Four typologies emerged from an analysis of these relationships. Round 3 revealed that controlled access via user authentication was preferred to all other regimes for both anonymized i.e. irretrievably delinked and coded genomic data involved children.

Discrepant beliefs in anonymization, and mistrust in the ability of existing data infrastructures to keep genomic data anonymized were primary sources of dissent that resulted in no consensus on Statements 10 and 11. Panelists' tendencies toward stricter access regimes coincided with the view that the risks of genomic data re-identification are significant despite promises of anonymity. Some panelists made this argument prospectively; that is, the anonymization myth was an impending future at the current pace of innovations in computational power. Other panelists, however, were convinced that anonymization is at present impossibility, and thereby warrants access controls categorically. These conclusions suggest that revising Statements 10 and 11 in ways that better align with stakeholder perceptions of anonymization may be needed to facilitate applicability of the KIDS framework to data sharing contexts cross-provincially and inter-institutionally.

Skepticism of anonymization made explicit in some panelist responses to Statements 10 and 11 directly affected the overall consensus and support for Statement 12. The lack of support was evident even after an amendment proposed to limit the obligation to provide families with data

sharing opportunities. The qualitative results for Statement 12 best illustrated how a breakdown in the triangulation of confidence influenced stakeholder perceptions regarding responsible oversight. Implicit in panelists' arguments was that data oversight bodies must trust in the epistemic and practical bases for genomic data security—of which anonymization is one technique—before endorsing data sharing opportunities with families. Confidence in the process and function of data anonymization—implicating the technical work arm in the triangulation confidence—was therefore a pre-requisite to endorsing data sharing opportunities for children and their families—the public engagement arm. Panelists may have in turn advocated for heightened data governance and oversight standards above what is permissioned in existing data protection regulations to compensate for lacking confidence in technical data securities as a result.

Clinician-scientists, however, unanimously advocated for open access to anonymized data and often used personal clinical experiences to support the ways in which data sharing enabled them to deliver better quality care for their patients. They argued only through aggregate, anonymized data availability and access could variant interpretation be possible with appropriate clinical follow up. They also contended that open access was especially pressing for children with rare genetic disease, in which it is often the case that few, if any children in the world harbor variants of interest that could be associated with their suspected disease. One panelist with a background in law also advocated for open access on these grounds. They based their rationale primarily on the justification that anonymized data poses minimal informational risks when weighed against the potential for (in)direct benefits that data sharing could generate for the child.

Panelists expressed that researchers bear the main responsibility for ensuring consent is obtained from patients and families, albeit they may not be those who do the consenting directly. Clinicians and other allied health professionals, including genetic counselors were recognized as key data sharing ambassadors within the circle of care, and as such served an important role in guiding patients and families through the consent process. Six primary resources were identified to support professionals in their consent of families, and were thematically categorized into technological, material and human resources. Research ethics and data access committees were referred most often as the most appropriate human resources responsible for data sharing oversight including, but not limited to data management and access.

Consequently, REC chairs and pediatric ethicists participating in the policy Delphi raised some of the strongest oppositions to open access regimes for anonymized data and likewise petitioned for strict user authentication criteria for all pediatric data considered identifiable. This

finding may shed light on an emerging tension between data sharing practitioners and oversight bodies. Although RECs should be responsible for data sharing oversight according to panelists, they also expressed that RECs required additional training and improved competencies to appropriately support researchers in consenting families on the realistic benefits and risks of sharing linked genomic and associated clinical data.

The areas of consensus and dissent analyzed in this policy Delphi have direct implications for achieving confidence in the technical work, data governance strategies and avenues for patient engagement involved in sharing linked genomic data, and which progress in the genomics-enabled learning health system depends. The 10 policy positions prioritized in this policy Delphi, as well as qualitative analysis nuancing the reasons for dissent in the remaining 3 positions help policy makers target areas for further policy negotiation, and additionally on what ethical-legal premises these negotiations require resolution. Consultation with patient stakeholders would be critical in this regard, if not essential for aligning data sharing policy with public values and priorities. Rapid shifts in the technical capacities that enable scientific progress in genomics and the data infrastructure sciences furthermore call for governance standards that are flexible to emerging innovations in both genomics and computer science. The framework proposed and validated in this study should be considered an initial seed from which Canadian data sharing policies involving children and other similarly vulnerable populations can continue to grow in an ethically-responsible data ecosystem.

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CHAPTER 6—Discussion, Conclusions, and Recommendations

This thesis identified responsible policies, practices and principles of data sharing and exchange in the pediatric genomics space. It asked two research questions to support the development of an ethical-legal framework for responsible data sharing in this context. First, *what ethical, legal, and social and scientific considerations enable responsible genomic and associated data sharing involving vulnerable patient populations, like children?* Chapter 1 defended twin ethical and scientific imperatives to share genomic data involving children, and proposed three responsibilities of proportionate governance toward this end: a responsibility to the data source, the data process, and to the data's anticipated impact. Because learning health systems embed clinical research and quality improvement directly into the patient care experience, research ethics oversight can be a requisite precursor to data sharing depending on the data's provenance, its proposed use and oversight. To best guide research ethics and other oversight committees, the systematic review of reasons presented in Chapter 2 identified what, and how such protections constitute responsible sharing of children's genomic and associated clinical data. The review of reasons corroborated many of the responsibilities outlined in Chapter 1, and further revealed the ways in which technical data infrastructures are leveraged to execute ethical-legal and social principles of responsible sharing therein.

Forty-three unique Types of Reasons were categorized into 5 overarching themes: 1) Children's Involvement; 2) Parent and family involvement, 3) Stakeholder involvement, 4) Benefits and risks and 5) Data Governance and Release. Limiting the scope of parental consent to authorize data sharing during childhood, and respecting children's right to be re-consented for continued use of their data once they reach the age of majority were the most strongly supported reasons for why and how data should be shared based on aggregate analysis of Reason Mentions. A policy position statement endorsing respect for children's right to consent to continued data sharing once they reach adulthood, along with 9 other policy position statements were then synthesized from the review findings. A consensus working group meeting of international pediatricians, genomic researchers, patient advocates and bioethics scholars further refined the policy position statements emerging from the systematic review to produce the initial Key Implications for Data Sharing (KIDS) framework.

To validate the draft KIDS framework in the Canadian context, a panel of Canadian data sharing stakeholders representing advocates and referees in law, research ethics, clinical ethics,

pediatric medicine and genomic research were engaged in three-round policy Delphi study. This exercise answered the second research question, *How do Canadian pediatricians, genomic researchers, ethicists and bioethical scholars prioritize the ethical-legal, social and scientific factors of genomic and associated clinical data sharing involving children in Canada?*

The panel reached consensus on 9 policy position statements based on mixed descriptive statistical and thematic content analyses. An additional statement was added to the KIDS Framework regarding the return of validated, clinically actionable genomic findings. Content analyses of the qualitative data, specifically, suggested that panelists prioritized three interrelated factors they reasoned constituted responsible data sharing governance in the pediatric data intensive sciences: i) security of the data's source, ii) oversight of its proposed uses and iii) access controls commensurate with the data's degree of sensitivity. Irreconcilable differences in panelists' views on informational risks, data access and oversight with respect to anonymized i.e. irretrievably delinked versus coded data involving children were primary sources of dissent identified at the end of 3 Delphi rounds. Statement 12 outlining a duty to afford children and their families the opportunity to share their genomic and associated clinical data also did not meet the conditions for consensus despite support for such a duty identified in the data sharing literature.

The final validated KIDS framework based on consensus parameters are presented in **Tables 25** and **26**, respectively. The policy Delphi study supported prior findings from the systematic review of reasons in a general sense. Namely, panelist ratings and feedback corroborated the central and normative importance of children's best interests, transparent consent and other governance processes, and the need to communicate realistic explanations of data sharing benefits and risks. Results from Statement 10 as well as Statement 12, however, directly refuted prior findings. Three overarching interpretations can be drawn from these negative results.

First, the majority position taken on Statement 10 that anonymized data be made available only through controlled access processes was inconsistent with the literature analyzed in the systematic review of reasons. This literature includes relevant data sharing policies/guidelines such as the Toronto Statement, which stipulates

> For aggregated data that cannot be used to identify individuals, databases are open access, but for clinical and genomic data that are associated with a unique, but not directly identifiable individual, access may be restricted. Under such conditions, arguments can be made for the release of data for studies involving human subjects, as doing so can augment the opportunities for new discoveries that could ultimately benefit individuals, communities, and society at large.

To test whether this effect was the result of definitional confusion, all subsequent surveys defined terms anonymization, coding, identifiability and other relevant terminologies directly in the prompts. Providing clarification on these definitions had little, to no effect on panelists' ratings. The conceptual map produced from Round 3 data quantified and qualified a second conclusion drawn from this study: the relative penetrance of what panelists referred to as the anonymization 'myth' and how perceived risks of data re-identifiability skew value judgments related to sharing children's data. Several hypotheses for this general skepticism concerning anonymization could be relevant when communicating the relative informational risks to non-scientific audiences including patients and families. The qualitative rationales provided by the most skeptical panelists also reinforced that re-identification risks dominated what should ideally be a balanced discussion of data sharing benefits and risks.

Concerns related to re-identifiability were unique to genomic data—and generally acknowledged for adults and children—yet panelists adopted a heightened sense of responsibility for protecting children from the negative consequences thereof. Greater concern for the potential negative consequences of anonymization, rather than the fidelity of anonymization techniques themselves may more accurately explain panelists' advocacy for added pediatric protections based on the qualitative rationales analyzed in the policy Delphi. While balancing informational risks and clinical benefits—direct, indirect or both—were widely invoked in the systematic review of reasons, only one panelist consistently discussed this balance in relation to responsible data access and governance. Moreover, clinicians represented the largest subgroup whose arguments in support of preferred access regimes and governance were anchored by the potential for clinical *benefit* as opposed to anticipated *risk*.

The anonymization myth also explains both the source and strength of dissent observed between typologies CAH1 and OAL mapped in **Figure 9.** While this dissent was primarily risk-oriented, the source and strength of dissent between typologies CAH2 and OAH was, in contrast, benefit-oriented. That is, opportunities for enhancing clinical knowledge were invoked to justify open access regimes for coded patient data.

Lastly, the result that training remains one of the most significant resource barriers to appropriate oversight of pediatric data sharing may suggest a lack of trust in current oversight mechanisms used to evaluate informational risks. Results from Round 3 brought this lack of professional competency into sharp relief, when the need for additional training and data-specific oversight and management expertise was most often recommended for research ethics committees

(RECs) over all other data governance stakeholders implicated in this study. Panelists instead recognized other necessary expertise and training opportunities that RECs were better placed to contribute. For example, they agreed that RECs help determine requirements for, and appropriate mechanisms of obtaining consent from children and their families to share data, when possible. Given current ambiguity in what activities fall under the ambit of ethics review versus quality improvement in the learning health system, research ethics boards will continue to play a central role in setting consent standards for data sharing as such learning systems mature.

Conceptual themes linking technical work, data governance and patient engagement produce a triangulation of confidence that can together explain how Canadian stakeholders construe responsible genomic and associated clinical data sharing involving children. These themes are taken up in the recommendations for policy detailed below, as well as accompanying directions for future research needed to move those policies from evidence to action related to data governance in the pediatric data-intensive sciences.

Recommendations

Anonymity is a shrinking practical reality according to many Canadian advocates and referees who served on the policy Delph panel. For them, anonymization i.e. irretrievably delinked genomic data was based on a false premise that individuals could not be re-identified with any reasonable likelihood. Researchers' inability to adequately anonymize genomic data, and keep children's data anonymous—the former a computational task while the latter an ongoing management and stewardship exercise—can compromise patient consent and ultimately trust in the pediatric data-intensive sciences. Panelists' views on anonymization translated into support for stricter data access controls than are currently outlined in existing clinical and research data protection guidelines e.g. Tri Council Policy Statement. The forte of this anonymization 'myth' points to possible paradigmatic shifts in thinking about data security at macro and micro levels of future policy development, respectively, where children's data may be taken up to support genomics-enabled learning health systems.

Macro-level recommendations for policy

Based on the combined findings of the systematic review in conversation with the policy Delphi study, the first recommendation this thesis makes for policy is to concentrate more resources on data accountability for unauthorized access and misuse as an intervention aimed at strengthening

data security and, in turn, trust and willingness to share data. This recommendation is predicated on a linear understanding of the data processing continuum pictured in **Figure 10**, beginning with 1) data production, 2) use and 3) exchange. Data security and management is, as Figure 10 shows, a cross-cutting theme and ongoing exercise.

Figure 10. Genomic and associated clinical data processing continuum

Content analyses performed on panelists' arguments from the policy Delphi unveiled that ethical-legal concerns regarding data security, and not data sharing per se, were at the core of panelists' skepticism in sharing anonymized data. This is a key conceptual difference that motivates intervening in data processing steps following data production, but preceding data exchange.

A focus on data security as the single point of intervention for responsible data sharing governance is, however, unsustainable. An assumption about theoretical limits of the contemporary arms race in data securities further informs this thesis' proposed emphasis on developing more robust data accountability policies. It is anticipated that no sooner will new systems approaches for keeping data secure will newer methods to exploit the vulnerabilities within them be introduced. This equilibrium between discovery and exploitation in the computational securities creates an arms race that continuously moves the target for proportionate data governance at a pace too rapid for concerted policy development and reform. The systematic review of reasons alludes to this arms race—in particular the finding that fulfilling ethical-legal obligations for data security increasingly relies on computation-mediated governance—as does one panelist's reflections on the future of computation and its impact on data ethics: "Technology is rapidly evolving and one can imagine, it [sic] the near future, that it will not be possible to guarantee anonymity, particularly where genetic data are concerned. Strict oversight by an independent research ethics committee may to the only means to provide protections for these research participants."

Unlawful infringement, data breach and (dis)respect for children as they are represented in their genomic and associated clinical data are more static socio-ethical phenomena upon which data

governance could act. Empirical policy and public perceptions research naturally follow from the proposal to prioritize data accountability in responsible data sharing governance. Namely, this thesis recommends further empirical policy work to articulate how punitive actions against data misuse and unauthorized access are determined, who enforces them, and can a two-prong accountability-security approach enhance public willingness and trust in data sharing from the perspectives of data contributors. Accountability for genomic and associated clinical data sharing involving children should mirror data involving adults in this respect.

There has been some movement towards an accountability-oriented approach to date. The Global Alliance for Genomics and Health, for example, endorsed an Accountability Policy with similar aims to broaden both the theoretical and practical foundations of genomic data privacy/security. The rationale for such a policy can be summarized in "If data stewards are not open about data availability and access processes, it is difficult to assess if data is fairly and effectively available. If data users do not take steps to demonstrate that use limitations are respected, it is difficult to assess if they are accountable for the data entrusted to them"(Global Alliance for Genomics and Health 2015).

Micro-level recommendations for policy

The areas of consensus identified in this policy Delphi study, in conversation with the 43 ethical-legal and social reasons for pediatric data sharing from the systematic review of reasons, informed four micro level i.e. practice- or institution-based recommendations. First, data governance and policy in pediatric genomics should be as interoperable as the genomic data itself. Panelists expressed how shared platforms should be developed to adhere to harmonized norms of data ethics oversight, facilitating more timely, secure and efficient data exchange. This recommendation can be challenging from a regulatory standpoint in jurisdictions like Canada with federated divisions of healthcare and health research oversight. A genomics-enabled learning health system indeed depends on such regulatory coherence to enable data mobilization across institutions and jurisdictional borders.

Capacity building through targeted training of those entities charged with data exchange oversight ensures data sharers respect the terms of consent made at the time of data contribution. Encouraging bioinformaticians and other data scientists to serve on oversight committees, including but not limited to research ethics and data access committees, helps to fill this competency gap. It is recommended that the next public consultation on revisions to the Tri Council Policy Statement

consider adding such data-centric expertise to Chapter 6, Article 6.4 outlining Basic REB Membership Requirements. A similar clause should be considered in the United States Common Rule, particularly in light of recent reforms towards centralizing ethics review for multi-site studies that the data intensive sciences such as genomics typify.

A third practice-based recommendation is to incorporate re-consent for continued use and sharing of children's data in the initial data sharing terms where possible. There is unequivocal support for re-contact/re-consent for pediatric data sharing in principle—notably in the biobanking literature as the systematic review of reasons corroborated—yet its logistical infeasibility limits widespread re-consent at the age of majority in practice. Certainly, myriad reasons complicate re-contacting children once they reach adults. Children could be lost to follow up when they transition to adult care, likely at a different healthcare institution; they may not be aware of their data contributions; or children may have died to name but a few real-world examples of such challenges to feasibility. A longitudinal, electronic health record which can travel with the patient across healthcare institutions and, ideally, across healthcare jurisdictions could greatly facilitate re-contact, to say nothing of the benefits to continuity of care. Even under ideal circumstnaces where children can be re-contacted, researchers may not be able to honor changes to the parents' initial data sharing decisions. This is often the reality if children's data were contributed anonymously and deposited in large, aggregate genomic databases.

The longitudinal accrual of informational benefits and risks from sharing genomic data has yet to be studied in depth from the perspectives of now-adult patients, highlighting the need for future research in this area to improve re-consent models for children once they reach the age of majority (see Bartha Maria Knoppers et al. 2016). Results from this thesis make evident, however, that uninformed *withdrawal* of the now-adult's data simply because this option is made available or potentially mandated is normatively equivalent to uninformed *consent* to the data's continued exchange. Adults whose data were contributed as children should have the opportunity to discuss the benefits and risks of their continued data use with the same comprehensiveness required at the time of initial consent.

It may be time to revise ethics governance standards with respect to i) anonymization of personal health information given advances in computation that challenge the fidelity with which data can remain anonymous; as well as the ii) categorical distinction between research and quality assurance/improvement when genomic and associated clinical data are used concurrently to drive the learning health system. Under Article 2.5 of the TCPS2, "Quality assurance and quality

improvement studies, program evaluation activities, and performance reviews, or testing within normal educational requirements when used exclusively for assessment, management or improvement purposes, do not constitute research for the purposes of this Policy, and do not fall within the scope of REB review"(Canadian Institutes of Health Research Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada. 2014). Activities that support genomics-enabled learning health systems meet the classification requirements for quality assurance/improvement. Yet, these activities can draw on research findings to inform new studies that aim to contribute new fundamental knowledge of the human genome, or to resolve existing clinical equipoise in precision health delivery. Learning health systems therefore fall in a grey area between classifications outlined in the TCPS2, one requiring ethics oversight while the other is exempt.

Two governance approaches may be feasible moving forward. Existing ethics review committees can treat all patient data required to support the data-intensive activities in the genomics-enabled learning health system as secondary use data. Explicit consent would not be required under Article 5.5A in this case, insofar as patients consented to the initial data collection needed for clinical care and an ethics review board granted approval for secondary use purposes. An alternative approach is to consider all data-intensive activities in the learning health system as quality assurance/improvement. This may be justifiable on the basis that such activities are needed to deliver the highest standard of care; the data collection/analysis poses no informational risks to patients above and beyond those already accepted in the course of clinical care; and the data processing procedures comply with existing clinical as well as research data protection regulations.

Finally, lack of representation from patients and families that limited the generalizability of this policy Delphi study highlights a potential strength of future empirical bioethics research that investigates public priorities in data ethics and governance. Namely, future research should aim to compare and contrast the ethical-legal priorities and decision-making considerations identified among those responsible for data governance with those articulated among patients and their families. This comparison would benefit from engaging both with prospective, as well as retrospective data contributors. Following data sharing decisions longitudinally across the life course, from initial data contribution as child patients through to adulthood would be an unprecedented opportunity to explore how sharing decisions and conceptions of data privacy/security evolve. It is uncontroversial that children born in the Internet age live in a data-rich world. Their familiarization and near-constant exposure to data as part of contemporary civic life, including data related to their

health, shape perceptions of where public-private digital boundaries lie for their personal information. Data governance should be evidence-based, yet responsive to these evolving sociotechnical realities.

Study Limitations

The interrelated studies that comprise this thesis are designed to be comprehensive pursuant to the thesis objectives, yet are not without some limitations. First, the policy Delphi did not benefit from explicit guidance in the literature as to how the method could be applied to studying bioethics policy. The thesis therefore piloted new applications of the method to study a new public policy making process. Expert representation is one area in which such methodological innovation had a limiting effect in this study. Given the multi-disciplinarity typified in bioethics, this policy Delphi did not achieve representation from all possible bioethics subdisciplines from which input on responsible data sharing in pediatric genomics could be beneficial. While the GAPH program is the largest national competition that supports infrastructure science and personalized medicine platforms in Canada, it is not reflective of all pediatric infrastructure science projects currently ongoing there. Research ethics review approval processes, and the terms of references for data access and sharing, for example, may differ for collaborators who participated in this study, particularly if they interacted with oversight bodies outside Canada. It is therefore possible that the views and experiences of panelists recruited from the 6 pediatric GAPH studies cannot be extrapolated to describe all policy-process links between ethics review and data sharing in Canada or elsewhere.

Canadian pediatric patients and parents of children who have shared their genomic and associated clinical data are two key stakeholder groups whose perspectives are missing from the policy Delphi. Their omission could challenge future stakeholder buy-in needed to effectively implement and operationalize the KIDS framework within actual patient care institutions. The overarching objectives of this thesis centered on studying data governance and its associated ethical-legal considerations justified their lack of involvement in part. For the purposes of studying the relationship between genomic data governance policies and practices, this thesis engaged with advocates and referees that were either actively involved in governing, or whose data sharing activities were subject to data governance rather than all possible stakeholders and beneficiaries of

pediatric data sharing thereof. Lower than expected response rates[xxviii] as well as the jurisdiction-specific focus similarly limited this study's generalizability beyond the Canadian contexts in which the thesis focused. Policy makers situated in jurisdictions where data governance may not rely on research ethics or data access committees should take this specific limitation into account.

Concluding Remarks

The overarching aim of this thesis was to understand the policies, processes and principles underlying responsible pediatric data sharing from the perspectives of data contributors, sharers and ethics oversight bodies in pediatric genomics in Canada. The need for policy-practice coherence in genomic and associated clinical data sharing can be accentuated when involving populations for whom such data may require special protections, such as children. From a normative understanding of responsible data sharing, the thesis developed and subsequently validated an ethical-legal framework to better enable such sharing: the Key Implications of Data Sharing (KIDS) framework in pediatric genomics. By identifying areas of Canadian-specific consensus and dissent on pediatric data sharing, the thesis offered recommendations and directions for future applied bioethics and health policy research to continue policy negotiation processes that support responsible, albeit proportionate data governance in the pediatric infrastructure sciences. It is hoped that the theoretical and practical contributions this thesis makes to responsible data sharing ensures present and future children in Canada remain at the forefront of healthcare systems that continuous 'learn' from the production, access and exchange of their genomic and associated clinical data.

[xxviii] The minimum sampling numbers published in existing methods papers available at the time of writing were met. It should be noted that sample sizes achieved in this study were comparably low to those reported in other policy Delphi studies published in the literature (see for example Klenk and Hickey 2012; Benton, González-Jurado, and Beneit-Montesinos 2013; Baker and Moon 2010; Baumann, Ervin, and Reynolds 1982; Adam Manley 2013; Gruber 2017).

CHAPTER 1

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CHAPTER 2

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Appendix A

Detailed search strategy applied in Medline, BIOSIS, Web of Science and Scopus for the systematic review of reasons of data sharing practices in pediatric genomics

Document updated:	Date: April 24, 2017	by	Genevieve Gore
Search strategy peer reviewed:	Date:	by	Genevieve Gore
Database searches conducted:	Date: October 26, 2016 (MEDLINE) April 21 & 24, 2017 (All)	by	Genevieve Gore
Database searches updated:	Date: April 21, 2017 (MEDLINE)	by	Genevieve Gore
Grey Literature searches conducted	Date: 11/28/18	by	Vasiliki Rahimzadeh

Databases/Trial registry	Platform	Dates	Notes
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily	Ovid	1946-present	
BIOSIS Previews, BIOSIS Previews Archive	Ovid	1926-2017 Week 21	
Web of Science	Web of Science	All timespans	
Scopus	Scopus	Inception-present	

Platform	Database(s)	# Results	Search Date	Saved (account)	Remarks
Ovid	MEDLINE	1359 records	2017/04/21	Vasiliki.rahimzadeh@mail.mcgill.ca	
Ovid	MEDLINE	1510 records	2018/11/28	Vasiliki.rahimzadeh@mail.mcgill.ca	Search that was run on April 21, 2017 contained errors:

					This version replaced it.
Ovid	BIOSIS	217 Records	2018/11/28	VR	
Web of Science	SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI	246 records	2018/11/28	VR	
Scopus	Scopus	396 records	2018/11/28	VR	

Records identified through database searching:
Records after duplicates removed:
Original searches

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily <1946 to Present>
Search Strategy:
---
1 exp Data Collection/ (1843584)
2 Databases, Genetic/ (17639)
3 exp Gene Library/ (37213)
4 *Biomedical Research/ (47767)
5 (big data or consorti* or open science or ((access* or collaborat* or releas* or share? or sharing) adj7 data) or biobank* or biorepositor*).ti,ab,kf. (63539)
6 or/1-5 (1992602)
7 exp Genome/ (889177)
8 (genetic* or genom* or "exome sequencing" or dna sequencing or gene or genes or hapmap or human haplotype map).ti,ab,kf. (2436823)
9 7 or 8 (2644811)
10 6 and 9 (128220)
11 10 not (exp animals/ not humans.sh.) (111836)
12 exp ethics/ (138044)
13 confidentiality/ (22221)
14 privacy/ (5748)
15 data protection/ (6375)
16 (es or lj).fs. (286798)
17 (ethic* or bioethics* or governance or assent* or opt* in or opt* out or reconsent* or re consent* or confidential* or privacy or private or autonom* or respect for persons or best interest*).ti,ab,kf. (367437)
18 12 or 13 or 14 or 15 or 16 or 17 (671761)
19 11 and 18 (4471)

20 exp child/ (1749645)
21 child$.mp. (2191833)
22 exp pediatrics/ (52868)
23 pediatric$.mp. (281984)
24 paediatric$.mp. (53552)
25 or/20-24 (2266981)
26 prematur*.mp. (184271)
27 preterm*.mp. (60589)
28 perinat$.mp. (68518)
29 neonat$.mp. (256271)
30 newborn$.mp. (701229)
31 new born$.mp. (3986)
32 infan$.mp. (1176898)
33 bab$.mp. (87912)
34 toddler$.mp. (8500)
35 boy$.mp. (135464)
36 girl$.mp. (130032)
37 kid$1.mp. (6986)
38 school$.mp. (276191)
39 juvenil$.mp. (82020)
40 underage$.mp. (1201)
41 under age$.mp. (4419)
42 teen$.mp. (26721)
43 minor$.mp. (268535)
44 youth$.mp. (63505)
45 pubescen$.mp. (1935)
46 adolescen$.mp. (1893147)
47 or/26-46 (3628409)
48 infan$.jw. (7558)
49 child$.jw. (141526)
50 pediatric$.jw. (375831)
51 paediatric$.jw. (55291)
52 adolescen$.jw. (38173)
53 or/48-52 (586793)
54 25 or 47 or 53 (4441634)
55 19 and 54 (1414)
56 remove duplicates from 55 (1371)
57 56 not ("20161027" or "20161028" or "20161029" or 2016103* or 2017*).dc. (1359)
58 56 not 57 (12)

****

Database: BIOSIS Previews <1969 to 2017 Week 21>, BIOSIS Previews Archive <1926 to 1968>
Search Strategy:
---
1 (big data or consorti* or open science or ((access* or collaborat* or releas* or share? or sharing) adj7 data) or biobank* or biorepositor*).mp. (55317)

2 (genetic* or genom* or "exome sequencing" or dna sequencing or gene or genes or hapmap or human haplotype map).mp. (5527458)
3 (ethic* or bioethics* or governance or assent* or opt* in or opt* out or reconsent* or re consent* or confidential* or privacy or private or autonom* or respect for persons or best interest*).mp. (407223)
4 child$.mp. (938561)
5 pediatric$.mp. (1512209)
6 paediatric$.mp. (22141)
7 4 or 5 or 6 (1662104)
8 prematur*.mp. (114429)
9 preterm*.mp. (47858)
10 perinat$.mp. (45922)
11 neonat$.mp. (190909)
12 newborn$.mp. (172464)
13 new born$.mp. (20266)
14 infan$.mp. (390564)
15 bab$.mp. (82052)
16 toddler$.mp. (4697)
17 boy$.mp. (81105)
18 girl$.mp. (68057)
19 kid$1.mp. (7077)
20 school$.mp. (105559)
21 juvenil$.mp. (147136)
22 underage$.mp. (461)
23 under age$.mp. (2082)
24 teen$.mp. (10906)
25 minor$.mp. (227347)
26 youth$.mp. (22166)
27 pubescen$.mp. (11474)
28 adolescen$.mp. (512014)
29 or/8-28 (1730453)
30 infan$.jw. (2546)
31 child$.jw. (62736)
32 pediatric$.jw. (235701)
33 paediatric$.jw. (26246)
34 adolescen$.jw. (10218)
35 or/30-34 (327827)
36 7 or 29 or 35 (2451863)
37 1 and 2 and 3 and 36 (115)
38 remove duplicates from 37 (104)

****

Web of Science
Exported from Web of Science on 2018-11-28
(TS=("data collection" OR "genetic database*" OR "gene librar*" OR "big data" OR consorti* OR "open science" OR biobank* OR biorepositor* OR ((access* OR collaborat*

OR releas* OR share* OR sharing) NEAR/7 data))) AND (TS=(genetic* OR genom* OR "exome sequencing" OR "dna sequencing" OR gene OR genes OR hapmap OR "human haplotype map")) AND (TS=(ethic* OR bioethics* OR governance OR assent* OR "opt* in" OR "opt* out" OR reconsent* OR "re consent*" OR confidential* OR privacy OR private OR autonom* OR "respect for persons" OR "best interest*")) AND (TS=(child* OR pediatric* OR paediatric* OR prematur* OR preterm* OR perinat* OR neonat* OR newborn* OR "new born*" OR infan* OR baby OR babyhood OR babies OR toddler* OR boy* OR girl* OR kid OR kids OR school* OR juvenil* OR underage* OR "under age*" OR teen* OR minor OR minors OR youth* OR pubescen* OR adolescen*) OR SO=(infan* OR child* OR pediatric* OR paediatric* OR adolescen*))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

****

Scopus
396 Records exported from Scopus on 2018-11-28

(TITLE-ABS-KEY ("data collection" OR "genetic database*" OR "gene librar*" OR "big data" OR consorti* OR "open science" OR biobank* OR biorepositor* OR ((access* OR collaborat* OR releas* OR share* OR sharing) PRE/7 data))) AND (TITLE-ABS-KEY (genetic* OR genom* OR "exome sequencing" OR "dna sequencing" OR gene OR genes OR hapmap OR "human haplotype map")) AND (TITLE-ABS-KEY (ethic* OR bioethics* OR governance OR assent* OR "opt* in" OR "opt* out" OR reconsent* OR "re consent*" OR confidential* OR privacy OR private OR autonom* OR "respect for persons" OR "best interest*")) AND (TITLE-ABS-KEY (child* OR pediatric* OR paediatric* OR prematur* OR preterm* OR perinat* OR neonat* OR newborn* OR "new born*" OR infan* OR baby OR babyhood OR babies OR toddler* OR boy* OR girl* OR kid OR kids OR school* OR juvenil* OR underage* OR "under age*" OR teen* OR minor OR minors OR youth* OR pubescen* OR adolescen*) OR SRCTITLE (infan* OR child* OR pediatric* OR paediatric* OR adolescen*))

Appendix B

Policy Delphi Surveys (Rounds 1-3).

Key Implications of Data Sharing in pediatric genomics (KIDS): policy Delphi ROUND 1

Key **I**mplications of **D**ata **S**haring in pediatric genomics: validating ethical-legal best practices for **KIDS**

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Ms. Rahimzadeh is supported by the Vanier Canada Graduate Scholarship (CIHR#359258)

FUNDING

Purpose

You have been identified as a relevant stakeholder (e.g. researcher, parent, patient advocate, policy maker, or research ethics review board member) in sharing genomic and associated clinical data involving children in Canada.

As such, your perspectives are valuable for **validating a Canadian policy framework that identifies the ethical, legal, social and scientific priorities necessary for sharing pediatric genomic and associated clinical data.**

Study procedures

You will be asked to participate in 3 rounds of online surveys over the course of the next 3 months. Round 1 of the survey, which you will be participating in today, involves evaluating 12 policy statements to support best practices for responsible data sharing involving chidren.

We kindly request that you complete Round 1 by: March 26th, 2018

Subsequent Rounds of surveys will be administered approximately every 4 weeks. The content of Rounds 2-4 will be based on your responses to this survey, and the responses of other key stakeholders who participate in the study. This method of research is called a policy Delphi, which

aims to highlight the policy implications and priorities of a diverse group of stakeholders on a public policy issue of interest (genomic and associated clinical data sharing in this case).

Benefits and Risks

While there may not be any direct benefit to you or a patient you know, your participation in this policy Delphi may help us chart the ethical-legal landscape of genomic and associated clinical data sharing in Canada. We do not anticipate any significant risk(s) to you as a result of your participation.

Withdrawal

To withdraw from the study, please contact the study lead, Vasiliki (Vaso) Rahimzadeh either by phone (514-887-7030) OR email (vasiliki.rahimzadeh@mail.mcgill.ca (mailto:vasiliki.rahimzadeh@mail.mcgill.ca)).

Confidentiality

All survey data will be hosted on a secure McGill server using LimeSurvey. Some results will also be analyzed in a qualitative database using N'Vivo software licensed privately to investigators Vaso Rahimzadeh (VR), Gillian Bartlett (GB) and Bartha Maria Knoppers (BMK). All data will be password protected to limit access only to the 3 investigators listed above. Moreover, all surveys responses administered online will remain strictly anonymous to all other participants. This means your name and contact will not be made available to anyone except for members of the research team. You will receive a personal "token" to access the online survey which is the only link between you and your survey responses.

You will be notified immediately by email in the event of any privacy breach experienced by the N'Vivo software, and the subsequent relocation of this data to an alternatively secured platform.

Participants' Rights

As a research participant in this study:

- you have the right to ask questions at any time
- your study participation is entirely voluntary
- your refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled
- you may discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled

Disclosure

By clicking 'next' after this page, you agree to participate in the study, acknowledge that the study has been explained to you, and your questions regarding the scope, purpose and extent of your participation have been answered to your satisfaction.

It is important to know that you do not waive any of your rights by consenting to participate in this survey. This consent form, as well as copies of all surveys can be printed directly from LimeSurvey for your records.

Thank you for your participation.

There are 30 questions in this survey

SAMPLE

In Round 1 of this Policy Delphi, you will be asked to evalaute 12 policy statements on sharing pediatric genomic and associated clinical data. Your evaluation for each statment will be based on **two** of the following factors: **relative importance**, **feasibility**, **desirability** or **relative confidence**.

We request that you provide a brief rationale for your evaluation in the comments box provided.

For the purposes of this policy Delphi, we take ***genomic and associated clinical data sharing*** to mean the broad exchange of genome sequencing data and related clinical/phenotypic descriptors from an individual pediatric patient, either as part of clinical care or research. Pediatric genomic and associated clinical data may include, but are not limited to: specific characterization of genetic variants and their associated clinical phenotypes; all whole genome/exome variants; and links to detailed genotyic and phenotypic profiles of pediatric patients and their unaffected family members.

A sample survey question and evaluation is provided for you below.

[]

▶SAMPLE

What is the **DESIRABILITY** of the following statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box:

Anonymized pediatric data should be made available via publicly accessible databases.

◯ **VERY DESIRABLE** [i.e. Will have a positive effect and little or no negative effect; Extremely beneficial; Justifiable on its own merit]

◯ **DESIRABLE** [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

◯ **UNDESIRABLE** [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

◯ **VERY UNDESIRABLE** [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

Please write your answer here:

Open access databases do not confer appropriate data protections, and only children who have reached the age of majority should authorize such sharing of their data once they are able to consent for themselves.

List of Statements

Below you fill find a complete list of all 12 statements. This list is accessible via the "Question index" tab throughout the survey.

[]

Key **I**mplications of **D**ata **S**haring (**KIDS**) in pediatric genomics

1. The best interests of children are primary.

2. Children should be listened to, and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways.

3. Parents should be informed in a transparent manner how their child's genomic and associated clinical data will be securely managed and used.

4. In a research context, data sharing infrastructures should enable children to withdraw consent to continued sharing of their genomic and associated clinical data when possible upon reaching the age of majority.

5. Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance.

6. Values conveyed by family, legal guardians or primary care givers should be respected when possible.

7. All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent.

8. The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits.

9. Duplicative collection of genomic research data involving pediatric patients should be avoided.

10. Anonymized pediatric data should be made available via publicly accessible databases.

11. Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process.

12. Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.

Demographics

[]

Which of the following stakeholder groups do you most closely identify with?

Choose one of the following answers

Please choose **only one** of the following:

- ◯ basic science researcher
- ◯ clinician researcher
- ◯ research ethics review board member
- ◯ privacy officer
- ◯ clinician
- ◯ policy maker
- ◯ parent/patient advocate
- ◯ clinical ethicist
- ◯ other [please explain in comments box]

Make a comment on your choice here:

[]

Which gender do you most closely identify with?

Please choose **only one** of the following:

- ◯ Female
- ◯ Male

Key Implications of Data Sharing (KIDS) Policy Statement #1

The best interests of children are primary.

[]

What is the **RELATIVE IMPORTANCE** of the above policy statement for responsibly sharing genomic and associated clinical data* involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY IMPORTANT [i.e. A highly relevant statement; First-order priority; Has direct bearing on the ability to share data involving pediatric patients in Canada; Must be addressed, adhered to, or recognized in all cases]

☐ IMPORTANT [i.e. A somewhat relevant statement; Second-order priority; Has an impact on the ability to share data involving pediatric patients in Canada, but not until other statements are addressed fully; Does not have to be fully resolved]

☐ SLIGHTLY UNIMPORTANT [i.e. An insignificant statement; Third-order priority; Has little impact on the ability to share data involving pediatric patients in Canada; Not a determining factor for the ability to share data involving pediatric patients in Canada]

☐ VERY UNIMPORTANT [i.e. Not at all relevant to sharing data involving pediatric patients in Canada; Not a priority]

[]

What is the **FEASIBILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #2

Children should be listened to, and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways.

[]

What is the **DESIRABILITY** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

[]

What is the **FEASIBILITY** of the above point to consider towards the responsible sharing of genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #3

Parents should be informed in a transparent manner how their child's genomic and associated clinical data will be securely managed and used.

[]

What is the **RELATIVE IMPORTANCE** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY IMPORTANT [i.e. A highly relevant statement; First-order priority; Has direct bearing on the ability to share data involving pediatric patients in Canada; Must be addressed, adhered to, or recognized in all cases]

☐ IMPORTANT [i.e. A somewhat relevant statement; Second-order priority; Has an impact on the ability to share data involving pediatric patients in Canada, but not until other statements are addressed fully; Does not have to be fully resolved]

☐ SLIGHTLY UNIMPORTANT [i.e. An insignificant statement; Third-order priority; Has little impact on the ability to share data involving pediatric patients in Canada; Not a determining factor for the ability to share data involving pediatric patients in Canada]

☐ VERY UNIMPORTANT [i.e. Not at all relevant to sharing data involving pediatric patients in Canada; Not a priority]

[]

What is the **RELATIVE CONFIDENCE** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ CERTAIN [i.e. Very confident this statement will facilitate responsible data sharing involving pediatric patients in Canada; You would be willing to make a decision to share data based solely on this point]

☐ RELIABLE [i.e. Somewhat confident this statement will facilitate responsible data sharing involving pediatric patients in Canada; You would be willing to make a decision to share data based on this statement and others (please specify which)]

☐ RISKY [i.e. Some risk that this statement may hinder responsible data sharing involving pediatric patients in Canada; You would be unwilling to make a decision based on this statement alone; Many incorrect inferences can be drawn from adopting this point]

☐ UNRELIABLE [i.e. Substantial risk that this statement would hinder responsible data sharing involving pediatric patients in Canada; Has no basis for your decision to share data]

Key Implications of Data Sharing (KIDS) Policy Statement #4

In a research context, data sharing infrastructures should enable children to withdraw consent to continued sharing of their genomic and associated clinical data when possible upon reaching the age of majority.

[]

What is the **DESIRABILITY** of the statement for responsibly sharing of genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

[]

What is the **FEASIBILITY** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #5

Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance.

[]

What is the **RELATIVE IMPORTANCE** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY IMPORTANT [i.e. A highly relevant statement; First-order priority; Has direct bearing on the ability to share data involving pediatric patients in Canada; Must be addressed, adhered to, or recognized in all cases]

☐ IMPORTANT [i.e. A somewhat relevant statement; Second-order priority; Has an impact on the ability to share data involving pediatric patients in Canada, but not until other statements are addressed fully; Does not have to be fully resolved]

☐ SLIGHTLY UNIMPORTANT [i.e. An insignificant statement; Third-order priority; Has little impact on the ability to share data involving pediatric patients in Canada; Not a determining factor for the ability to share data involving pediatric patients in Canada]

☐ VERY UNIMPORTANT [i.e. Not at all relevant to sharing data involving pediatric patients in Canada; Not a priority]

[]

What is the **DESIRABILITY** of the statement for responsily sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

Key Implications of Data Sharing (KIDS) Policy Statement #6

Values conveyed by family, legal guardians or primary care givers should be respected when possible.

[]

What is the **RELATIVE IMPORTANCE** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY IMPORTANT [i.e. A highly relevant statement; First-order priority; Has direct bearing on the ability to share data involving pediatric patients in Canada; Must be addressed, adhered to, or recognized in all cases]

☐ IMPORTANT [i.e. A somewhat relevant statement; Second-order priority; Has an impact on the ability to share data involving pediatric patients in Canada, but not until other statements are addressed fully; Does not have to be fully resolved]

☐ SLIGHTLY UNIMPORTANT [i.e. An insignificant statement; Third-order priority; Has little impact on the ability to share data involving pediatric patients in Canada; Not a determining factor for the ability to share data involving pediatric patients in Canada]

☐ VERY UNIMPORTANT [i.e. Not at all relevant to sharing data involving pediatric patients in Canada; Not a priority]

[]

What is the **FEASIBILITY** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and

funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #7

All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent.

[]

What is the **DESIRABILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

[]

What is the **FEASIBILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #8

The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits.

[]

What is the **FEASIBILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

[]

What is the **RELATIVE CONFIDENCE** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ CERTAIN [i.e. Very confident this statement will facilitate responsible data sharing involving pediatric patients in Canada; You would be willing to make a decision to share data based solely on this point]

☐ RELIABLE [i.e. Somewhat confident this statement will facilitate responsible data sharing involving pediatric patients in Canada; You would be willing to make a decision to share data based on this statement and others (please specify which)]

☐ RISKY [i.e. Some risk that this statement may hinder responsible data sharing involving pediatric patients in Canada; You would be unwilling to make a decision based on this statement alone; Many incorrect inferences can be drawn from adopting this point]

☐ UNRELIABLE [i.e. Substantial risk that this statement would hinder responsible data sharing involving pediatric patients in Canada; Has no basis for your decision to share data]

Key Implications of Data Sharing (KIDS) Policy Statement #9

Duplicative collection of genomic research data involving pediatric patients should be avoided.

[]

What is the **DESIRABILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

[]

What is the **FEASIBILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #10

Anonymized pediatric data should be made available via publicly accessible databases.

[]

What is the **DESIRABILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

[]

What is the **FEASIBILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #11

Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process.*

*An intermediate tier of data access between 'open' (no restrictions to access) and 'controlled' (also referred to as 'managed access' and involves established restrictions to certain types of data or by certain types of users e.g. clinicians, researchers etc).

[]

What is the **DESIRABILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

[]

What is the **FEASIBILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Key Implications of Data Sharing (KIDS) Policy Statement #12

Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.

[]

What is the **DESIRABILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]

☐ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]

☐ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]

☐ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

[]

What is the **FEASIBILITY** of the above statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box.

*

Comment only when you choose an answer.
Please select one answer

Please choose all that apply and provide a comment:

☐ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]

☐ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]

☐ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]

☐ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Statement changes?

[]

What changes, if any, would you make to the existing statements to enable responsible sharing of genomic and associated clinical data involving children?

Please write your answer here:

1. The best interests of children are primary

2. Children should be listened to and involved in discussion-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways.

3. Parents should be informed in a transparent manner how information regarding their child will be securely managed and used.

4. In a research context, data sharing infrastructures should enable children to withdraw consent when possible upon reaching the age of majority.

5. Parental authorization for ongoing, or future unspecified research should include the provision of information related to existing data governance

6. Values conveyed by family, legal guardians or primary care givers should be respected when possible.

7. All professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks and discuss these with parents at the time of consent.

8. The decision to share pediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits.

9. Duplicative collection of research data involving pediatric patients should be avoided.

10. Anonymized pediatric data should be made available via publicly accessible databases.

11. Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or restricted access process.

12. Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.

Additional statements?

[]

What additional features of "responsible" data sharing, if any, should be included in the KIDS Framework that are not currently addressed by one of the existing statements?

Please write your answer here:

Thank you for your participation. You will receive the results of Round 1, and a link to participate in Round 2 of this Policy Delphi in approximtely 4 weeks.

06-06-2020 – 00:00

Submit your survey.
Thank you for completing this survey.

ROUND 3 Key Implications of Data Sharing (KIDS) in pediatric genomics policy Delphi

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Funding	Ms. Rahimzadeh is supported by the Vanier Canada Graduate Scholarship (CIHR#359258)

Dear participant,

Welcome back and thank you for contributing to Rounds 1 and 2 of this Policy Delphi. Your continued engagement is greatly appreciated to preserve the scientific integrity of this study.

The complete results, including composite ratings and qualitative responses from Rounds 1 and 2 are available for your reference on my project website (www.projectpedigree.org) and linked here (http://www.projectpedigree.org/results-summary-round-2/).

PURPOSE

Your participation in this third and final round of the policy Delphi will take approximately 10 minutes and will involve the following. We ask that you kindly complete Round 3 by **Monday, October 15th, 2018.**

1. Qualifying the relationships between mechanisms of data access, oversight and benefits/risks for sharing irretrievably delinked e.g. anonymized data

Individual ratings and qualitative responses indicated low consensus and strong polarization on the desirability of sharing irretrievably delinked i.e. anonymized data and its appropriate terms of access. You will be asked to review the group's responses, and qualify your own views on how the ability to irretrievably delink data influences (if at all) your ethical-legal considerations for access and governance.

2. Qualifying the relationships between mechanisms of data access, oversight and benefits/risks for sharing coded data

Individual ratings and qualitative responses indicated low consensus and moderate polarization on the desirability of sharing coded data and its appropriate terms of access. You will be asked to review the group's responses, and qualify your own views on how coding pediatric data influences (if at all) your ethical-legal considerations for access and governance.

3. Exploring roles and responsibilities

One statement indicated considerable divergence on the entities responsible for providing children and parents the opportunity to share their data. You will be asked to review the group's responses, and qualify your views on what roles (if any) various stakeholders have in providing this opportunity.

DISCLOSURE

By clicking 'next' after this page, you agree to participate in the study, acknowledge that this phase of the study has been explained to you, and your questions regarding the scope, purpose and extent of your participation have been answered to your satisfaction.

It is important to know that you do not waive any of your rights by consenting to participate in this survey. As a research participant in this study:

- you have the right to ask questions at any time
- your study participation is entirely voluntary
- your refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled
- you may discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled

This form, as well as copies of all surveys can be printed directly from LimeSurvey for your records.

There are 11 questions in this survey

Data access and governance for sharing irretrievably delinked pediatric data

The ratings and rationales collected from 12 respondents during Round 2 on sharing anonymized pediatric data are provided below. For the purposes of this Round, '*anonymization*' refers to the irreversible de-linking of identifying information from associated genomic data. By '*identifying information*', we mean sources of data that alone, or in combination with other information may reasonably be expected to identify an individual.

[]

	Respondent ratings (N = 12)				
ANONYMIZED PEDIATRIC DATA SHOULD BE MADE AVAILABLE VIA PUBLICLY ACCESSIBLE DATABASES	**Very desirable [1]**	**Desirable [2]**	**Undesirable [3]**	**Very Undesirable [4]**	**Average rating**
	5	2	3	2	2.17
	Definitely feasible [1]	**Possibly feasible [2]**	**Possibly not feasible [3]**	**Definitely not feasible [4]**	**Average rating**
	5	3	4	0	1.92

Adopt statement (n = 6)	• Denying families the ability to help other children (and possibly their own child as well) by sharing genomic and associated clinical data is paternalistic and can be seen as violating their autonomy. • The TCPS considers anonymized data to present minimal risk to participants, and children can have illnesses and social issues that pediatric-specific data collection. The risks to children in collecting and making available data (with protections considered adequate for adults) are not unreasonable, nor does the level of risk alone justify restricting its use. • Anonymized data is very low risk; the significant risk is related to lack of data sharing when it comes to children and slowing the field of research. • De-linking protects individual confidentiality while putting valuable data in the public domain; Such data is good for the quality of aggregate data but not for individual medical care
Eliminate statement (n = 6)	• Children cannot make this decision for themselves • True anonymity does not exist with the level of granularity contained within large genetic datasets. • There are a number of issues that makes this a difficult statement to implement and uphold, including technical aspects like the quality and format of data, processes to maintain updating of relevant linked clinical phenotype information, governance related to access. Only adult data should be accessed this way • Risks of re-identification are too great and data types are too variable to have a blanket statement.

[]

What is the most desirable mechanism of data access to **irretrievably delinked i.e. anonymized** genomic data involving children?

*

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Open access
- ◯ Controlled access via user authentication
- ◯ No access
- ◯ Other [ ]

Anonymisation: The irreversible delinking of identifying information from associated data.

Controlled/ Restricted Access: Access to data that is subject to conditions and an approval process.

Data: Observations, narratives or measurements that are assumed as the basis for further analysis, calculation or reasoning.

Open data access: Making data available without restrictions.

[]

Which of the following lends the most appropriate oversight for responsible sharing of **irretrievably delinked i.e. anonymized** genomic and associated clinical data involving children? *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Research ethics review committee
- ◯ Data access committee
- ◯ Clinicians
- ◯ Principal Investigators
- ◯ Other

Coding/ Pseudonymisation: The act of replacing an identifier with a code for the purpose of avoiding direct identification of the participant, except by persons holding the key linking the code and identifier.

Controlled/ Restricted Access: Access to data that is subject to conditions and an approval process.

Data: Observations, narratives or measurements that are assumed as the basis for further analysis, calculation or reasoning.

Data Access Committee: A committee that reviews and authorizes applications for data access and use.

Research Ethics Review Committee: An autonomous body that is mandated by the institution to review the ethical acceptability of research involving humans according to regulations relevant in the jurisdiction in which the research takes place.

[]
Please provide a brief rationale for your choices above considering how, if at all, the ability to irretrievably delink children's genomic data influences your views on informational benefits/risks of sharing.

*

Please write your answer here:

Data access and governance for sharing coded pediatric data

The ratings and rationales collected from 12 respondents during Round 2 on sharing coded pediatric data are provided below. For the purposes of Round 3, we refer to 'coding/coded data' as replacing an identifier with a unique key to avoid direct identification of the patient/participant, except by persons holding this key linking the code with the identifier. By 'controlled access', we mean access to data that is subject to conditions and an approval process.

[]

IDENTIFIABLE PEDIATRIC GENOMIC AND ASSOCIATED CLINICAL DATA SHOULD BE CODED AND MADE AVAILABLE THROUGH A CONTROLLED ACCESS PROCESS* * amended from *Identifiable pediatric genomic and associated clinical data should be coded and made available through a controlled or registered access process*	**Rating (n = 12)**				
	Very Desirable [1]	**Desirable [2]**	**Undesirable [3]**	**Very Undesirable [4]**	**Average rating**
	8	1	1	2	1.75
	Definitely Feasible [1]	**Possibly Feasible [2]**	**Possibly Not Feasible [3]**	**Definitely Not Feasible [4]**	**Average rating**
	4	5	2	1	2
Amend the statement (n = 5)	• The best approach would be anonymized data made available through a controlled access process, but this approach is certainly more desirable than anonymized public access.				

Keep the original statement (n = 4)	• It is important to know who is accessing data and why it is being accessed. • Again this is about not overprotecting children and [not] delaying research. • Registered can be more efficient and economical for access to data but its potential benefits depend on the robustness of the applicant authentication process.
Eliminate the statement (n = 3)* *The original Round 2 questionnaire did not indicate an option to eliminate the statement. Three votes to eliminate the statement were tallied based on qualitative analysis of the responses.	• Both the original and amended statement raise significant concerns. The risks have not been well enough established, and the statement is premature. • I disagree with the idea of having identifiable data made available, even through a controlled process.

[]
What is the most desirable mechanism of data access for **coded** genomic and associated clinical data involving children? *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Open access
- ◯ Controlled access via user authentication
- ◯ No access
- ◯ Other [ ]

Coding/ Pseudonymisation: The act of replacing an identifier with a code for the purpose of avoiding direct identification of the participant, except by persons holding the key linking the code and identifier.

Controlled/ Restricted Access: Access to data that is subject to conditions and an approval process.

Data: Observations, narratives or measurements that are assumed as the basis for further analysis, calculation or reasoning.

Identifiable/ Personal Data: Data that alone or in combination with other data may reasonably be expected to identify an individual.

[]
Which of the following lends the most appropriate oversight for responsible sharing of **coded** genomic and associated clinical data involving children? *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Research ethics review committee
- ◯ Data access committee
- ◯ Clinicians
- ◯ Principal Investigators
- ◯ Other [ ]

Coding/ Pseudonymisation: The act of replacing an identifier with a code for the purpose of avoiding direct identification of the participant, except by persons holding the key linking the code and identifier.

Controlled/ Restricted Access: Access to data that is subject to conditions and an approval process.

Data: Observations, narratives or measurements that are assumed as the basis for further analysis, calculation or reasoning.

Data Access Committee: A committee that reviews and authorizes applications for data access and use.

Research Ethics Review Committee: An autonomous body that is mandated by the institution to review the ethical acceptability of research involving humans according to regulations relevant in the jurisdiction in which the research takes place.

[]

Please provide a brief rationale for your choices above considering how, if at all, preserving an identifiable link to children's genomic and associated clinical data influences your views on informational benefits/risks of sharing. *

Please write your answer here:

Providing opportunities to share irretrievably delinked and coded data

The ratings and rationales collected from 12 respondents during Round 2 on the obligation to provide data sharing opportunities to children and their families are provided below.

[]

PROVIDING CHILDREN AND THEIR FAMILIES THE OPPORTUNITY TO SHARE THEIR GENOMIC AND ASSOCIATED CLINICAL DATA IS AN OBLIGATION OF RESEARCHERS*.	**Rating (n = 12)**				
	Very desirable [1]	**Desirable [2]**	**Undesirable [3]**	**Very Undesirable [4]**	**Average rating**
	8	1	2	1	1.67
*amended from *Providing children and their families the opportunity to share their genomic and associated clinical data is an obligation of those who generate such data*	**Definitely Feasible [1]**	**Possibly Feasible [2]**	**Possibly Not Feasible [3]**	**Definitely Not Feasible [4]**	**Average rating**
	3	2	2	5	2.5

Agree with amendment (n = 4)	• [Providing children and families the opportunity to share data] would be an undue burden on clinicians but makes eminent sense for researchers. • The TCPS considers anonymized data to present minimal risk to participants, and children can have illnesses and social issues that merit pediatric-specific data collection. The risks to children in collecting and making available data (with protections considered adequate for adults) are not unreasonable, nor does the level of risk alone justify restricting its use. • Anonymized data is very low risk; the significant risk is related to lack of data sharing when it comes to children and slowing the field of research. • De-linking protects individual confidentiality while putting valuable data in the public domain; Such data is good for the quality of aggregate data but not for individual medical care
Disagree with amendment (n = 5)	• My clinical practice is consumed by doing genomic testing on patients, as is that of many of my pediatric specialty colleagues. Restricting data sharing to the narrow silo of researchers is going to miss vast amounts of highly valuable information, directly relevant to clinical practice. • Childhood cancer has gone from a universally fatal disease to one with about 95% survival in a generation because of data sharing amongst clinicians. • How is researcher defined? • This statement is directed at clinical labs, not just researchers who increasingly recognize and are required by their funders to share genomic data. • More sequencing will be done in children clinically than through research within a few years. • Data from the medical care context is equally important for better science.

Neither agree nor disagree (N = 3)* *The original questionnaire did not include this option. Three votes to eliminate the statement were tallied based on qualitative analysis of the responses during Round 2.	• I disagree with the concept of an obligation in principle. • Not all researchers have the means to achieve [providing families and children the opportunity to share data]. • Data sharing is not appropriate for all types of genomic research. • There is no obligation even if highly desirable.

[]Which of the following stakeholders are responsible for consenting children and their families about the opportunity to give their permission to share genomic and associated clinical data? Check all that apply and briefly describe the role they play in the consent process. *

Comment only when you choose an answer.

Please choose all that apply and provide a comment:

- ☐ Research ethics review committees
- ☐ Data access committees
- ☐ Clinical laboratories
- ☐ Clinicians
- ☐ Principal investigators
- ☐ Genetic counsellors
- ☐ Allied health professionals
- ☐ Clinical ethicists
- Other:

[]
What resources and infrastructures are needed to properly support the professional(s) you selected above in providing children and their families with opportunities to share their data? *

Please write your answer here:

Many thanks for your participation and continued support of this study! Stay up-to-date on all study-related publications and conference presentations on my project website

www.projectpedigree.org (http://www.projectpedigree.org/)

Submit your survey.
Thank you for completing this survey.

Key implications of data sharing in pediatric genomics (KIDS) policy Delphi ROUND2

Thank you for agreeing to participate in Round 2 of this Policy Delphi!

Your thoughts and continued engagement are greatly appreciated. Complete results from Round 1, including composite ratings and qualitative responses for each of the 12 Statements reviewed are available for your reference on my project website (www.projectpedigree.org) and are linked here (http://www.projectpedigree.org/ratings/).

PURPOSE

Your participation in Round 2 of the policy Delphi will involve:

1. Assessing 6 Polarized Statements

Six of the 12 individual statements reviewed during Round 1 indicated some degree of polarization and/or lack of consensus based on a combined analysis of the overall ratings and qualitative responses. You will be asked to re-rate each of these six statements in Round 2 after reviewing the group's responses.

2. Assessing 4 Amendments

Four amendments to the original KIDS Framework were proposed in Round 1, which you will be asked to adopt or reject.

3. Evaluating 1 new statement

One additional statement was proposed during Round 1. You will be asked to rate the proposed statement on the basis of Desirability and Feasibility, and decide on its formal inclusion in the KIDS Framework.

DISCLOSURE

By clicking 'next' after this page, you agree to participate in the study, acknowledge that this phase of the study has been explained to you, and your questions regarding the scope, purpose and extent of your participation have been answered to your satisfaction.

It is important to know that you do not waive any of your rights by consenting to participate in this survey. As a research participant in this study:

- you have the right to ask questions at any time
- your study participation is entirely voluntary
- your refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitle
- you may discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled

This form, as well as copies of all surveys can be printed directly from LimeSurvey for your records.

There are 16 questions in this survey

Round 1 Results [Parental Authorization]

The overall ratings and rationales from 10 respondents are provided for the statement below:

PARENTAL AUTHORIZATION FOR ONGOING, OR FUTURE UNSPECIFIED RESEARCH SHOULD INCLUDE THE PROVISION OF INFORMATION RELATED TO EXISTING DATA GOVERNANCE

Please indicate your ratings for **RELATIVE IMPORTANCE** and **DESIRABILITY** after reviewing the group's responses.

[]

GROUP RATINGS				GROUP AVERAGE
[1]	[2]	[3]	[4]	
Very Important	Important	Unimportant	Very Unimportant	
6	2	2	0	1.6
Definitely Desirable	Possibly Desirable	Undesirable	Definitely Undesirable	
5	4	0	1	1.7

Reasons for strong support

- Ideal that this happens to allow a governance structure to enable future research
- This information is central to the risk/benefit profile presented by the decision
- Governance is key. At the highest level within the 'system', all involved should know the desired best practices are desired and ensure systems are in place to see these upheld.
- Facilitates future use of data
- This ensures participates (parents) are engaged in future research

Reasons for weak support

- It is better to obtain broader consent form the outset for data that will be accessible beyond a single study
- Will have a neutral effect, not necessarily a major detriment nor a significant benefit

Reasons for weak opposition

- While this information is important, it should be accessible but not necessarily imposed as it can increase the density of the consent.

- Specific consent is required for all research use, including unspecified future research
- This only applies to tightly-held databases with very limited access

Reasons for strong opposition

- This information needs to be publicly posted & accessible, but not necessarily targeted to parents

*

Please write your answer(s) here:

Relative Importance

Desirability

Please enter your ratings in the boxes provided using the following scales:

1—Very important, Very Desirable

2—Somewhat important, Desirable

3—Somewhat unimportant, Undesirable

4—Very unimportant, Very Undesirable

Round 1 Results [Family Values]

The overall ratings and rationales from 10 respondents are provided for the statement below:

VALUES CONVEYED BY FAMILY, LEGAL GUARDIANS OR PRIMARY CARE GIVERS SHOULD BE RESPECTED WHEN POSSIBLE

Please indicate your ratings for **RELATIVE IMPORTANCE** and **FEASIBILITY** after reviewing the group's responses.

[]

GROUP RATINGS				GROUP AVERAGE
[1]	[2]	[3]	[4]	
Very Important	Important	Unimportant	Very Unimportant	
5	3	2	0	1.7
Definitely Feasible	Possibly Feasible	Possibly Not Feasible	Definitely Not Feasible	
2	2	4	2	2.6

Reasons for strong support

- This is central to the consent process; absent this commitment the process is meaningless
- No reason why it should *not* be taken into account

Reasons for weak support

- Unclear how this could be achieved clinically or in most research since there is not a menu of data sharing options—simply yes or no.
- There is a natural attrition such that those that value sharing are in research projects so this statement is not as important based on that fact.
- The need to maintain relationships with individual sea have the resource to continue to revisit findings are implementation challenges

Reasons for weak opposition

- Difficult to define and communicate values, particularly when they conflict between the child and their family

- Values are dynamic
- Either value data sharing or not—it should be all in, or all out

Reasons for strong opposition

- If a participant has strong values that would potentially make them uncomfortable about the use of their data, they should probably not authorize future sharing at all
- Beyond consent, this is too cumbersome to accurately track

Please write your answer(s) here:

Relative Importance

Feasibility

Please enter your ratings in the boxes provided using the following scales:

1—Very Important, Definitely Feasible

2—Somewhat Important, Possibly Feasible

3—Somewhat Unimportant, Possibly Not Feasible

4—Very Unimportant, Definitely Not Feasible

[]
In your view, what (if anything) could be done to enhance the FEASIBILITY of this statement?

*

Please write your answer here:

Round 1 Results [Benefits & Risks]

The overall ratings and rationales from ten respondents are provided for the statement below:

ALL PROFESSIONALS INVOLVED IN PROCESSES OF DATA SHARING AND DATA-INTENSIVE RESEARCH HAVE THE RESPONSIBILITY TO BALANCE POTENTIAL BENEFITS AND RISKS AND DISCUSS THESE WITH PARENTS AT THE TIME OF CONSENT

Please indicate your ratings for **DESIRABILITY** and **FEASIBILITY** after reviewing the group's responses.

[]

GROUP RATINGS				GROUP AVERAGE
[1]	[2]	[3]	[4]	
Very Desirable	Desirable	Undesirable	Very Undesirable	
5	3	1	1	1.8
Definitely Feasible	Possibly Feasible	Possibly Not Feasible	Definitely Not Feasible	
2	4	2	2	2.4

Reasons for Strong Support

- Consent should be a 'living' agreement and not just viewed as a one off event, especially in the on-going follow-up and management of patients.
- This is central to the responsible conduct of research and research ethics.
- This is standard practice.
- We do this already, with no hindrances to implementation

Reasons for Weak Support

- To the degree possible, this supports informed consent
- Ongoing involvement and assessment, follow up of natural history, evolution of a clinical phenotype, will require resources.
- Implementation is context-dependent

- It will require resources and more training as many researchers, companies, etc. are reluctant to engage in these discussions or provide for the requisite infrastructure to ensure data privacy and safety.

Reasons for Weak Opposition

- Many consenting processes are sub-optimal and researchers tend not to want to spend adequate time
- The "all" is problematic in this statement, will be hard to operationalize
- The responsibility rests with the person obtaining consent

Reasons for Strong Opposition

- All professionals? While communication is primary, this level could very well be overwhelming.
- Yes to those involved in data sharing, but those doing data research may have no relationship to study participants

*

Please write your answer(s) here:

Desirability

Feasibility

Please enter your ratings in the boxes provided using the following scales:

1—Very Desirable, Definitely Feasible

2—Desirable, Possibly Feasible

3—Undesirable, Possibly Not Feasible

4—Very Undesirable, Definitely Not Feasible

[]

In your view, what (if anything) could be done to enhance the FEASIBILITY of this statement?

*

Please write your answer here:

Amendment [Benefits & Risks]

Please indicate whether you agree or disagree to the following amendment (in red) proposed by respondents during Round 1, and provide a brief rationale for your choice:

[]

~~ALL~~ PROFESSIONALS INVOLVED IN CONSENT PROCESSES RELATED TO DATA SHARING AND DATA-INTENSIVE RESEARCH HAVE THE RESPONSIBILITY TO BALANCE POTENTIAL BENEFITS AND RISKS. A TRAINED DESIGNATE SHOULD BE AVAILABLE TO DISCUSS THESE WITH PARENTS AT THE TIME OF CONSENT. *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Agree and amend
- ◯ Disagree and keep original statement

Make a comment on your choice here:

***Summary of changes:**

1) Remove "all" professionals,

2) specify that responsibility to balance benefits and risks lies with those involved in consent, and

3) propose that a "trained designate" be available to discuss benefits and risks with parents during the consent process.

Round 1 Results [Anonymized Pediatric Data]

The overall ratings and rationales from ten respondents are provided for the statement below:

ANONYMIZED PEDIATRIC DATA SHOULD BE MADE AVAILABLE VIA PUBLICLY ACCESSIBLE DATABASES

Please indicate your ratings for **DESIRABILITY** and **FEASIBILITY** after reviewing the group's responses.

[]

GROUP RATINGS				GROUP AVERAGE
[1]	[2]	[3]	[4]	
Very Desirable	Desirable	Undesirable	Very Undesirable	
4	3	2	1	2
Definitely Feasible	Possibly Feasible	Possibly Not Feasible	Definitely Not Feasible	
3	4	3	0	2

Reasons for Strong Support

- Extremely beneficial to enhance knowledge
- This approach is likely the most feasible because it requires the least oversight.
- Implementation is dependent on data type

Reasons for Weak Support

- Jurisdictional differences [in data protection and governance] may hinder implementation.
- It really helps to know if a variant of unknown significance could be a clinically relevant finding based on other similar cases.
- Consent requirements

Reasons for Weak Opposition

- Though there are clear benefits to pursue this for adults, the risks outweigh the benefits when it comes to children.
- Controlled access to which researchers must apply is preferable.

- The technicality will not be the issue—rather, what is the governance framework to manage this beast. When experts are having a hard time interpreting findings, some of what could be publicly available lacks sufficient quality upon which to made clinical decisions. And once the data is posted, how will new information around interpretation be provided?

Reasons for Strong Opposition

- Availability of data should only be linked to purpose, considering recent data breaches involving Facebook and Google.

*

Please write your answer(s) here:

Desirability

Feasibility

Please enter your ratings in the boxes provided using the following scales:

1—Very Desirable, Definitely Feasible

2—Desirable, Possibly Feasible

3—Undesirable, Possibly Not Feasible

4—Very Undesirable, Definitely Not Feasible

Amendment [Anonymized Pediatric Data]

Please indicate whether you agree or disagree to eliminate the following statement from the KIDS Framework as proposed by respondent(s) during Round 1, and provide a brief rationale for your choice:

[]

ANONYMIZED PEDIATRIC DATA SHOULD BE AVAILABLE VIA PUBLICLY ACCESSIBLE DATABASES *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Agree and eliminate
- ◯ Disagree and keep original statement

Make a comment on your choice here:

Summary of change: Eliminate statement on anonymized pediatric data sharing

Round 1 Results [Identifiable Pediatric Data]

The overall ratings and rationales from ten respondents are provided for the statement below:

IDENTIFIABLE PEDIATRIC GENOMIC AND ASSOCIATED CLINICAL DATA SHOULD BE CODED AND MADE AVAILABLE THROUGH A CONTROLLED OR REGISTERED ACCESS PROCESS.

Please indicate your ratings for **DESIRABILITY** and **FEASIBILITY** after reviewing the group's responses.

[]

GROUP RATINGS				GROUP AVERAGE
[1]	[2]	[3]	[4]	
Very Desirable	**Desirable**	**Undesirable**	**Very Undesirable**	
7	1	1	1	1.6
Definitely Feasible	**Possibly Feasible**	**Possibly Not Feasible**	**Definitely Not Feasible**	
4	5	0	1	1.8

Reasons for Strong Support

- A great model that is better than our bottlenecked environment
- Needed and justified on its own merits

Reasons for Weak Support

- Not identifiable but perhaps anonymized data

Reasons for Weak Opposition

- The proposed data use could be potentially re-identifying when combined with other databases and in ways that we may not appreciate at this time.
- An REB would require very detailed information to adjudicate such a request; doubtful that most REBs would be equipped to assess risk

*

Please write your answer(s) here:

Desirability

Feasibility

Please enter your ratings in the boxes provided using the following scales:

1—Very Desirable, Definitely Feasible

2—Desirable, Possibly Feasible

3—Undesirable, Possibly Not Feasible

4—Very Undesirable, Definitely Not Feasible

Amendment [Identifiable Pediatric Data]

Please indicate whether you agree or disagree to the following amendment (in red) proposed by respondent(s) during Round 1, and provide a brief rationale for your choice:

[]

IDENTIFIABLE PEDIATRIC GENOMIC AND ASSOCIATED CLINICAL DATA SHOULD BE CODED AND MADE AVAILABLE THROUGH A CONTROLLED ~~OR REGISTERED~~ ACCESS PROCESS. *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Agree and amend
- ◯ Disagree and keep original statement

Make a comment on your choice here:

Summary of change: Remove "registered access" as an option for sharing identifiable pediatric genomic and associated clinical data.

Round 1 Results [Data Sharing Obligation]

The overall ratings and rationales from ten respondents are provided for the statement below:

PROVIDING CHILDREN AND THEIR PARENTS THE OPPORTUNITY TO SHARE GENOMIC AND ASSOCIATED CLINICAL DATA IS AN OBLIGATION OF THOSE WHO GENERATE SUCH DATA

Please indicate your ratings for **DESIRABILITY** and **FEASIBILITY** after reviewing the group's responses.

[]

GROUP RATINGS				GROUP AVERAGE
[1]	[2]	[3]	[4]	
Very Desirable	**Desirable**	**Undesirable**	**Very Undesirable**	
4	3	2	1	2
Definitely Feasible	**Possibly Feasible**	**Possibly Not Feasible**	**Definitely Not Feasible**	
3	2	4	1	2.3

Reasons for Strong Support

- This would be ideal and a significant incentive for children and families to participate in date "donation."
- Providing opportunity important - but does not obligate them to do so [share data].

Reasons for Weak Support

- Resourcs required to make feasible
- One does not want to put families in the situation of requiring that they share. And there must be supports within the health care system for clinicians at the front line to support this work.
- It is less clear that clinicians are obligated to provide this opportunity, since the data in question is being collected for clinical reasons and should be given room to make that judgment.

Reasons for Weak Opposition

- This may limit those who want to do smaller, less complex projects if sharing is an obligation.
- The obligation is to the patient not to process
- Not all grants have the resources to do this
- The consent process in the context of clinical genomics is already very onerous.
- Explaining the complexities of genetic analysis to lay people is difficult and time consuming.
- Adding data sharing increases the difficult. It is possible, but will almost certainly require additional resources in busy clinical environments.

Reasons for Strong Opposition

- Children and parents have no such obligations

*

Please write your answer(s) here:

Desirability

Feasibility

Please enter your ratings in the boxes provided using the following scales:

1—Very Desirable, Definitely Feasible

2—Desirable, Possibly Feasible

3—Undesirable, Possibly Not Feasible

4—Very Undesirable, Definitely Not Feasible

[]

In your view, what (if anything) could be done to enhance the FEASIBILITY of this statement? *

Please write your answer here:

Amendment [Data Sharing Obligation]

Please indicate whether you agree or disagree with the following amendment (in red) proposed by respondent(s) during Round 1, and provide a brief rationale for your choice:

[]

PROVIDING CHILDREN AND THEIR PARENTS THE OPPORTUNITY TO SHARE GENOMIC AND ASSOCIATED CLINICAL DATA IS AN OBLIGATION OF ~~ALL PROFESSIONALS WHO GENERATE SUCH DATA~~ RESEARCHERS.

*

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Agree and amend
- ◯ Disagree and keep original statement

Make a comment on your choice here:

*__Summary of change:__ Obligate ONLY researchers (rather than all professionals e.g. clinicians) to provide children and their parents the opportunty to share their data.

New statement

Please evaluate the **DESIRABILITY** and **FEASIBILITY** of the following statement proposed during Round 1 for inclusion in the KIDS Framework.

INCIDENTAL (SECONDARY) FINDINGS OF CLINICALLY ACTIONABLE, VALIDATED GENOMIC RESULTS SHOULD BE MADE AVAILABLE

[]
What is the **DESIRABILITY** of the statement for responsibly sharing genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box. *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ VERY DESIRABLE [i.e. Will only have a positive effect; Extremely beneficial; Justifiable on its own merit]
- ◯ DESIRABLE [i.e. Will have a positive effect and little or no negative effect; Beneficial; Justifiable as a by-product or in combination with other statements]
- ◯ UNDESIRABLE [i.e. Will have a negative effect; Risky; May be justified only as a by-product of a different statement]
- ◯ VERY UNDESIRABLE [i.e. Will have a major negative effect; Extremely risky; Unjustifiable in all cases]

Make a comment on your choice here:

[]
What is the **FEASIBILITY** of the above statement towards the responsible sharing of genomic and associated clinical data involving children in Canada? Please provide a brief justification for your choice in the comments box. *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ DEFINITELY FEASIBLE [i.e. No expected hindrance to implementation; Few to no additional resource requirements; Imposes few to no burden(s) on stakeholders; Acceptable to the majority of researchers, institutions, patients and funders]
- ◯ POSSIBLY FEASIBLE [i.e. Some expected hindrance but still implementable; Some additional resources required; Further consideration or preparation required to secure stakeholder buy-in]
- ◯ POSSIBLY NOT FEASIBLE [i.e. Some indication that implementation is unworkable; Significant unanswered questions regarding implementation]
- ◯ DEFINITELY NOT FEASIBLE [i.e. Cannot be implemented; Unmanageable resource demands; Unworkable; Significant stakeholder resistance either expected or demonstrated]

Make a comment on your choice here:

New statement adoption

Should the new statement below be adopted into the KIDS Framework?

[]

INCIDENTAL (SECONDARY) FINDINGS OF CLINICALLY ACTIONABLE, VALIDATED GENOMIC RESULTS SHOULD BE MADE AVAILABLE *

Choose one of the following answers

Please choose **only one** of the following:

- ◯ Agree and adopt new statement
- ◯ Disagree and reject new statement

Make a comment on your choice here:

Thank you for your participation. You will receive the results of Round 2, and a link to participate in Round 3 of this Policy Delphi in approximtely 6 weeks.

Vasiliki Rahimzadeh, PhD Candidate

Department of Family Medicine; Centre of Genomics and Policy

McGill University

Vasiliki.rahimzadeh@mail.mcgill.ca (mailto:Vasiliki.rahimzadeh@mail.mcgill.ca)

514-887-7030

INVESTIGATORS Gillian Bartlett, PhD (co-supervisor)

Associate Professor, Department of Family Medicine

McGill University

Bartha Maria Knoppers, PhD (co-supervisor)

Director, Centre of Genomics and Policy

McGill University

FUNDING Ms. Rahimzadeh is supported by the Vanier Canada Graduate Scholarship (CIHR#359258)

Submit your survey.
Thank you for completing this survey.

Appendix C

McGill University Institutional Review Board Approval for KIDS Policy Delphi study

McGill Faculty of Medicine

Institutional Review Board
- CONTINUING REVIEW FORM -

The completed form is to be submitted electronically to submit2irb.med@mcgill.ca. The continuing review form must be received at least **one (1) month** before the expiration of the last ethics approval. If you require additional information, please visit the IRB website at: http://www.mcgill.ca/medresearch/ethics/ or by calling 514-398-3124.

Principal Investigator	Gillian Bartlett
Faculty and Department	Medicine/Family Medicine
Study Coordinator, if applicable	NA
Address:	5858 Cotes des Neiges, Suite 300, Montreal H3S 1Z1
E-mail	gillian.bartlett@mcgill.ca Telephone: 514-399-9100
Study Title	Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?
Grant title, if different from study title.	
IRB Study Number	A04-E32-16B Date of last approval 4-29-16
Has there been a change or addition to the financial support for this study?	☐ YES ◉ NO
If yes, please specify the changes/additions.	

Status of the Protocol

- ☑ Active enrolment
- ☐ Recruitment complete
- ☐ Recruitment on hold
- ☐ Data analysis
- ☐ Secondary Analysis only
- ☐ Inactive/dormant**

When did this study begin? 9-1-16

**If the study is inactive/ dormant (i.e., there are no participants enrolled in the study and no study activity is occurring), please specify the reason:

If the study is is actively enrolling participants, or if enrolment is complete, please answer the following questions:

Study sample size:	~40	Total number enrolled in the study:	3

Number of participants that have completed this study:	0	Total number of participants withdrawn	0
Projected date of completion of study enrolment:	5-31-18	Projected date of study completion:	5-1-19

Please provide a brief description of what has occurred since the IRB's last ethics approval.

A systematic literature review has been conducted and a manuscript prepared for publication as a precursor to field work planned as part of this doctoral thesis. Participants have been identified, and preliminary email notifications sent to local investigators that will be included in the study. Duing to participant availability and emerging scholarly advancements in the field of data governance/ethics, the sequence of study activities and projected timelines for completion have been modified accordingly. The majority of fieldwork for the study, and

Has the study revealed any new findings or knowledge relevant to the potential benefits and/or study risks that may influence participants' willingness to continue in the study?

- ☐ YES
- ☐ NO
- ◉ N/A

Has this new information been communicated to participants?

- ☐ YES
- ☐ NO
- ◉ N/A

If applicable, please describe the findings.

Has an amendment(s) to the protocol been submitted to the IRB in the past year?

- ☐ YES
- ◉ NO

What is the version date of the most recent IRB- approved protocol? 4-29-16

Has the consent form(s) been revised in the past year?

- ☐ YES
- ◉ NO
- ☐ N/A

Have consent form modifications been reported to the IRB?

- ☐ YES
- ☐ NO
- ◉ N/A

Version date/s of the most recently approved consent form(s): 4-29-16

Have any adverse events occurred since the last approval?

- ☐ YES
- ☐ NO
- ◉ N/A

If yes, how many at McGill sites?

How many at all sites?

Have the adverse events been reported to the IRB? If no, submit all adverse events with this form.

- ☐ YES
- ☐ NO
- ◉ N/A

Have there been any publications?

- ◉ YES
- ☐ NO

If yes, append list: Rahimzadeh V. Sharing outside the sandbox? A child ' s right to an open future for data sharing. (2016). In:

SIGNATURES

Principal Investigator Date

IRB Chair Date

McGill

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

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

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

April 29, 2016

Dr. Gillian Bartlett
Department of Family Medicine
5858 Chemin de la Cote des Neiges – Suite 300
Montreal, Quebec H3S 1Z1

RE: IRB Study Number A04-E32-16B
Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?

Dear Dr. Bartlett,

Our office has received the application for ethics review of the above study, on behalf of your PhD candidate, Vasiliki Rahimzadeh.

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 an expedited approval for the study (April 2016) is provided by the IRB Chair on April 29, 2016. The ethics certificate for this study is valid until **April 2017**. The study proposal will be presented for corroborative approval at the next meeting of the Institutional Review Board, at which time a certification document will be issued.

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 **April 2017**. Please inform the IRB promply of any modifications that may occur to the study over the next twelve months.

Sincerely,

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

April 17, 2018

Dr. Gillian Bartlett
Department of Family Medicine
5858 Chemin de la Cote des Neiges, Suite 300
Montreal, QC H3S 1Z1

RE: IRB Study Number A04-E32-16B
Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?

Dear Dr. Bartlett,

Thank you for submitting an application for Continuing Ethics Review for the above-referenced study.

The study progress report was reviewed and an expedited re-approval was provided by the Co-Chair on April 17, 2018. The ethics certification renewal is valid from **April 27, 2018 to April 26, 2019**.

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld and / or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly. Regulation does not permit the implementation of study modifications prior to IRB review and approval.

Regards,

Carolyn Ells, PhD
Co-Chair
Institutional Review Board

cc: V. Rahimzadeh
A04-E32-16B

McGill Faculty of Medicine

Institutional Review Board
- CONTINUING REVIEW FORM -

The completed form is to be submitted electronically to submit2irb.med@mcgill.ca. The continuing review form must be received at least **one (1) month** before the expiration of the last ethics approval. If you require additional information, please visit the IRB website at: http://www.mcgill.ca/medresearch/ethics/ or by calling 514-398-3124.

Principal Investigator: Gillian Bartlett

Faculty and Department: Medicine/Family Medicine

Study Coordinator, if applicable: Vasiliki Rahimzadeh (PhD student)

Address: 5858 Cotes des Neiges, Suite 300
Montreal, QC

E-mail: gillian.bartlett@mcgill.ca Telephone: 514-399-9100

Study Title: Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?

Grant title, if different from study title.:

IRB Study Number: A04-E32-16B Date of last approval: 04/27/2018

Has there been a change or addition to the financial support for this study? ○ YES ◉ NO

If yes, please specify the changes/additions.

Status of the Protocol

- [x] Active enrolment — When did this study begin? 05/16/2016
- [ ] Recruitment complete
- [ ] Recruitment on hold
- [x] Data analysis
- [ ] Secondary Analysis only
- [ ] Inactive/dormant**

RECEIVED
McGill University
MAR - 8 2018
FACULTY OF MEDECINE
IRB

**If the study is inactive/ dormant (i.e., there are no participants enrolled in the study and no study activity is occurring), please specify the reason:

If the study is is actively enrolling participants, or if enrolment is complete, please answer the following questions:

Study sample size: 40 Total number enrolled in the study: 3

Number of participants that have completed this study: 0

Total number of participants withdrawn: 0

Projected date of completion of study enrolment: 05/01/2018

Projected date of study completion: 05/01/2019

Please provide a brief description of what has occurred since the IRB's last ethics approval.

A systematic review has been completed, and recruitment of key stakeholders in pediatric data sharing is currently ongoing for the second phase of this phd dissertation research. The second phase involves a series of online surveying as part of a policy delphi, the first round of which was sent to participants on February 28th, 2018. Of 40 participants sent the study protocol, consent form and link to the Round 1 survey, 1 participant has completed the Round 1 survey in full. Data collection/analysis for Round 1 has commenced, and will

Has the study revealed any new findings or knowledge relevant to the potential benefits and/or study risks that may influence participants' willingness to continue in the study?

- ○ YES
- ○ NO
- ◉ N/A

Has this new information been communicated to participants?

- ○ YES
- ○ NO
- ◉ N/A

If applicable, please describe the findings.

Has an amendment(s) to the protocol been submitted to the IRB in the past year?

- ○ YES
- ◉ NO

What is the version date of the most recent IRB- approved protocol?

Has the consent form(s) been revised in the past year?

- ○ YES
- ◉ NO
- ○ N/A

Have consent form modifications been reported to the IRB?

- ○ YES
- ○ NO
- ◉ N/A

Version date/s of the most recently approved consent form(s):

Have any adverse events occurred since the last approval?

- ○ YES
- ○ NO
- ◉ N/A

If yes, how many at McGill sites?

How many at all sites?

Have the adverse events been reported to the IRB? If no, submit all adverse events with this form.

- ○ YES
- ○ NO
- ◉ N/A

Have there been any publications?

- ○ YES
- ◉ NO

If yes, append list:

SIGNATURES

Principal Investigator: Gillian Bartlett Digitally signed by Gillian Bartlett Date: 2018.03.08 17:10:22 -05'00' Date: 03/08/2018

IRB Chair: Carolyn Ells Date: Apr 17, 2018

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

April 4, 2017

Dr. Gillian Bartlett
Department of Family Medicine
5858 Chemin de la Cote des Neiges – Suite 300
Montreal, Quebec H3S 1Z1

RE: IRB Study Number A04-E32-16B
Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?

Dear Dr. Bartlett,

Thank you for submitting an application for Continuing Review for the above-referenced study.

The study progress report was reviewed and full Board re-approval was provided on April 3, 2017. The ethics certification renewal is valid from **April 28, 2017 to April 27, 2018.**

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld and / or the study's data may be revoked for failing to comply with this requirement.

Should any modification or unanticipated development occur prior to the next review, please notify the IRB promptly.

Sincerely,

Serge Gauthier, MD
Interim Co-Chair
Institutional Review Board

cc: V. Rahimzadeh
A04-E32-16B

McGill Faculty of Medicine

Institutional Review Board
- CONTINUING REVIEW FORM -

The completed form is to be submitted electronically to submit2irb.med@mcgill.ca. The continuing review form must be received at least **one (1) month** before the expiration of the last ethics approval. If you require additional information, please visit the IRB website at: http://www.mcgill.ca/medresearch/ethics/ or by calling 514-398-3124.

Principal Investigator	Gillian Bartlett
Faculty and Department	Medicine/Family Medicine
Study Coordinator, if applicable	NA
Address:	5858 Cotes des Neiges, Suite 300, Montreal H3S 1Z1
E-mail	gillian.bartlett@mcgill.ca Telephone: 514-399-9100
Study Title	Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?
Grant title, if different from study title.	
IRB Study Number	A04-E32-16B Date of last approval 4-29-16
Has there been a change or addition to the financial support for this study?	○ YES ◉ NO
If yes, please specify the changes/additions.	

Status of the Protocol

- ☑ Active enrolment — When did this study begin? 9-1-16
- ☐ Recruitment complete
- ☐ Recruitment on hold
- ☐ Data analysis
- ☐ Secondary Analysis only
- ☐ Inactive/dormant**

RECEIVED
McGill University
FEB 16 2017
FACULTY OF MEDECINE
IRB

**If the study is inactive/ dormant (i.e., there are no participants enrolled in the study and no study activity is occurring), please specify the reason:

If the study is is actively enrolling participants, or if enrolment is complete, please answer the following questions:

Study sample size:	~40	Total number enrolled in the study:	3

Number of participants that have completed this study: 0

Total number of participants withdrawn: 0

Projected date of completion of study enrolment: 05/31/2018

Projected date of study completion: 05/01/2019

Please provide a brief description of what has occurred since the IRB's last ethics approval.

A systematic literature review has been conducted and a manuscript prepared for publication as a precursor to field work planned as part of this doctoral thesis. Participants have been identified, and preliminary email notifications sent to local investigators that will be included in the study. Due to participant availability and emerging scholarly advancements in the field of data governance/ethics, the sequence of study activities and projected timelines for completion have been modified accordingly. The majority of fieldwork for the study, an

Has the study revealed any new findings or knowledge relevant to the potential benefits and/or study risks that may influence participants' willingness to continue in the study?

- ○ YES
- ○ NO
- ◉ N/A

Has this new information been communicated to participants?

- ○ YES
- ○ NO
- ◉ N/A

If applicable, please describe the findings.

Has an amendment(s) to the protocol been submitted to the IRB in the past year?

- ○ YES
- ◉ NO

What is the version date of the most recent IRB- approved protocol?

Has the consent form(s) been revised in the past year?

- ○ YES
- ◉ NO
- ○ N/A

Have consent form modifications been reported to the IRB?

- ○ YES
- ○ NO
- ◉ N/A

Version date/s of the most recently approved consent form(s):

Have any adverse events occurred since the last approval?

- ○ YES
- ◉ NO
- ○ N/A

If yes, how many at McGill sites?

How many at McGill?

DATE OF I.R.B. APPROVAL

APR 3 - 2017

Faculty of Medicine
McGill University

Have the adverse events been reported to the IRB? If no, submit all adverse events with this form.

- ○ YES
- ○ NO
- ◉ N/A

Have there been any publications?

- ○ YES
- ○ NO

If yes, append list:

Rahimzadeh V. Sharing outside the sandbox? A child's right to an open future for data sharing. (2016). In:

SIGNATURES

Principal Investigator: Gillian Bartlett

Digitally signed by Gillian Bartlett
Date: 2017.02.16 12:13:47 +01'00'

Date: 02/16/2017

IRB Chair

Date: 2017/APR/03

McGill

Faculty of Medicine
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Montreal, QC H3G 1Y6

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

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Tél/Tel: (514) 398-3124

May 10, 2019

Dr. Gillian Bartlett
Department of Family Medicine
5858 Chemin de la Cote des Neiges, Suite 300
Montreal, QC H3S 1Z1

RE: IRB Study Number A04-E32-16B – Re-activated
Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?

Dear Dr. Bartlett,

We have re-activated your study further to your submission of the Continuing Review Form for the above-referenced study.

The study progress report was reviewed and an expedited re-approval was provided by the Chair on May 10, 2019. The renewed ethics certificate is valid from **May 10, 2019 to April 24, 2020.** The re-approval of the ethics oversight for this study will be reported at the next meeting of the Institutional Review Board on June 10, 2019.

The Investigator is reminded of the requirement to report all IRB approved protocol and consent form modifications to the Research Ethics Offices (REOs) for the participating hospital sites. Please contact the individual hospital REOs for instructions on how to proceed. Research funds may be withheld, and/or the study's data may be revoked for failing to comply with this requirement.

If any study modifications or unanticipated study developments occur prior to the next annual review, including study terminations, please notify the IRB promptly. Regulation does not permit the implementation of study modifications prior to IRB review and approval.

Regards,

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: V. Rahimzadeh
A04-E32-16B

McGill Faculty of Medicine

Institutional Review Board
- CONTINUING REVIEW FORM -

The completed form is to be submitted electronically to submit2irb.med@mcgill.ca. The continuing review form must be received at least **one (1) month** before the expiration of the last ethics approval. If you require additional information, please visit the IRB website at: http://www.mcgill.ca/medresearch/ethics/ or by calling 514-398-3124.

Principal Investigator	Gillian Bartlett
Faculty and Department	Medicine/Family Medicine
Study Coordinator, if applicable	
Address:	5858 Cotes des Neiges, Suite 300 Montreal, QC
E-mail	gillian.bartlett@mcgill.ca
Telephone:	514-399-9100
Study Title	Evaluating the gap between research ethics review and data sharing in the pediatric infrastructure sciences: a case of big data and little ethics?
Grant title, if different from study title.	
IRB Study Number	A04-E32-16B
Date of last approval	04/27/2018

Has there been a change or addition to the financial support for this study? ○ YES ◉ NO

If yes, please specify the changes/additions.

Status of the Protocol

- ☐ Active enrolment
- ☑ Recruitment complete
- ☐ Recruitment on hold
- ☑ Data analysis
- ☐ Secondary Analysis only
- ☐ Inactive/dormant**

When did this study begin? 04/27/2018

RECEIVED
McGill University
MAY 10 2019
FACULTY OF MEDECINE
IRB

**If the study is inactive/ dormant (i.e., there are no participants enrolled in the study and no study activity is occurring), please specify the reason:

If the study is is actively enrolling participants, or if enrolment is complete, please answer the following questions:

Study sample size:	
Total number enrolled in the study:	12

Number of participants that have completed this study:

Total number of participants withdrawn

Projected date of completion of study enrolment:

Projected date of study completion: 12/31/2019

Please provide a brief description of what has occurred since the IRB's last ethics approval.

Has the study revealed any new findings or knowledge relevant to the potential benefits and/or study risks that may influence participants' willingness to continue in the study?

- ○ YES
- ◉ NO
- ○ N/A

Has this new information been communicated to participants?

- ○ YES
- ○ NO
- ◉ N/A

If applicable, please describe the findings.

Has an amendment(s) to the protocol been submitted to the IRB in the past year?

- ○ YES
- ◉ NO

What is the version date of the most recent IRB- approved protocol?

Has the consent form(s) been revised in the past year?

- ○ YES
- ◉ NO
- ○ N/A

Have consent form modifications been reported to the IRB?

- ○ YES
- ○ NO
- ◉ N/A

Version date/s of the most recently approved consent form(s):

Have any adverse events occurred since the last approval?

- ○ YES
- ○ NO
- ◉ N/A

If yes, how many at McGill sites?

How many at all sites?

DATE OF I.R.B. APPROVAL
MAY 10 2019
Faculty of Medicine
McGill University

Have the adverse events been reported to the IRB? If no, submit all adverse events with this form.

- ○ YES
- ○ NO
- ◉ N/A

Have there been any publications?

- ◉ YES
- ○ NO

If yes, append list: Rahimzadeh, V. Sharing outside the sandbox? A child's right to an open future for data sharing. In: Verma M, +

SIGNATURES

Principal Investigator

Digitally signed by Gillian Bartlett
Date: 2019.05.10 14:52:39 -04'00'

Date: May 10, 2019

IRB Chair

Date: May 10, 2019

McGill

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

Faculté de médecine
3655, Promenade Sir William Osler #633
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Tél/Tel: (514) 398-3124

May 1, 2019

Dr. Gillian Bartlett
Department of Family Medicine
5858 Chemin de la Cote des Neiges, Suite 300
Montreal, QC H3S 1Z1

RE: IRB Study Number A04-E32-16B – Lapsed – Terminated
Evaluating the gap between research ethics review and data sharing in pediatric infrastructure science: a case of big data and little ethics?

Dear Dr. Bartlett,

Following a review of studies held by the Institutional Review Board of the Faculty of Medicine, it has come to our attention that the ethics certificate for the above-mentioned study expired on April 26, 2019.

The Institutional Review Board made repeated attempts to contact you without success. In the absence of an application for continuing review, our office is terminating the ethics oversight for this study.

The termination will be reported to the Full Board at the next scheduled meeting of the Institutional Review Board. In order to re-activate the study, you will have to re-submit an Initial Review form and all of the pertinent documentation.

Regards,

Roberta Palmour, PhD
Chair
Institutional Review Board

cc: V. Rahimzadeh
A04-E32-16B