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Key Implications of Data Sharing in Pediatric Genomics

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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.

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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 genotyic 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 (eg, 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 provide 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 Framework 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.

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 otherwise, 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.

Box 1. Points to Consider for the Responsible Sharing of Pediatric Genomic and Associated Phenotypic Data

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.

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 develop-

mentally 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 neonates 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 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 (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 context 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 informed 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 caregivers should be respected when possible (Box 1). The informed consent 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 unknown 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 shar-

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.

ing 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 diagnostic 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 disease 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**).

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 reasonable 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 throughout 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 stakeholder 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 collaboration 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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