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Genome-Wide Sequencing for Unexplained Developmental Disabilities and Multiple Congenital Anomalies — Project Protocol, Ethics, Patients' Perspectives, and Experiences Section

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

HTA	Health Technology Assessment
WES	whole exome sequencing
WGS	whole genome sequencing

Introduction and Rationale

The use of precision genomic techniques is growing in the clinical setting, with many applications aiming to solve and provide a mechanism for the diagnosis for rare undiagnosed or difficult to diagnose conditions.[1,2]

Unexplained developmental disabilities and multiple congenital anomalies are terms that describe the presentation of a range of potentially overlapping symptoms.[3,4] These symptoms can be attributed to several conditions, including global developmental delay and intellectual disability.[3,4] Approximately 1% of Canadians are reported to have a developmental disability.[5] Further, approximately 3% of babies in the developed world are born with some congenital anomaly, which can coincide with developmental delay and intellectual disability.[6,7] Rare diseases, currently defined in Canada as those presenting in less than 5 in 10,000,[8] collectively affect about one in 12 Canadians, and may also present similar or overlapping challenges.[8] In suspected cases, early detection is critical to ensure timely access to appropriate care. However, because of complex presentation and multifactorial etiology, diagnostic challenges are common.[4,9,10]

Genome-wide sequencing (whole exome and genome sequencing) involves the broad evaluation and detection of genetic variants. This technology may play a role when conditions with potential underlying genetic causes are difficult to diagnose using traditional approaches. Whole exome sequencing (WES) is a technique based on the evaluation of protein-coding regions of the genome.[11,12] These regions contain the majority of mutations that contribute to health conditions of genetic origin.[11] The sequencing process generates information that is compared to genetically typical references to identify disease-linked variations and to help establish a diagnosis.[11] Whole genome sequencing (WGS), on the other hand, reports on the entire genome. These approaches are considered more comprehensive than more targeted genetic testing approaches such as single-gene testing or chromosomal microarray.[11,12]

Interest in genome-wide sequencing in the context of the described conditions is attributed to its potential role in solving the “diagnostic odyssey.” This term is used to describe a difficult and potentially unresolved journey to diagnosis.[13] This phenomenon is common in the case of rare diseases, particularly those without a family history, or with multifactorial causes where the condition is not yet traced to a specific gene or genes.[14] Novel sequencing techniques show promise for addressing a notable gap in care and have demonstrated clinical utility in several genetic conditions[15,16] but may not provide clarity in all circumstances.[17] There are numerous considerations surrounding the potential adoption of the technology. Questions have been raised regarding the risk and handling of misdiagnosis and incidental findings, and how to address findings for which there is no treatment option.[15] There is also concern regarding the potential cascade of downstream diagnostic and treatment costs that can be triggered by test results.[15] Issues of data ownership and privacy, informed consent, and the potential for genetic discrimination have also been discussed.[15,18]

Genome-wide sequencing is currently conducted in a research capacity in Canada, primarily at academic centres.[19] Recently, there has been increased demand for services — in part, due to a growing awareness and declining costs — resulting in more requests for out-of-country care.[15,20,21] While costs are dropping, the technology would likely be at an additional cost to standard of care and there is uncertainty about potential downstream cost savings.[22] Expanding access would require resources to support the procurement and operation of the technology, trained clinic and laboratory staff, appropriate facilities, and other supports (e.g., access to genetic counselling), which may not be available in all contexts.[23] Accordingly,

there is interest in assessing the place of WES and WGS within diagnostic pathways for relevant clinical conditions, and in determining the appropriate criteria for patient selection and access to care.

Policy Question(s)

Should genome-wide sequencing for the diagnosis of patients with unexplained developmental disabilities and multiple congenital anomalies be publicly funded?

Objective

The objective of this HTA is to address the policy questions through an assessment of the relevant multi-disciplinary evidence.

CADTH, in collaboration with Health Quality Ontario, is conducting a Health Technology Assessment (HTA) on the use of genome-wide sequencing for patients with unexplained developmental disabilities and multiple congenital anomalies. Health Quality Ontario will complete a systematic review of clinical evidence, an economic evaluation, a budget impact analysis, and direct patient engagement interviews for patients' preferences and values. CADTH will conduct a rapid review of qualitative literature on patients' and health care providers' perspectives and experiences, and an analysis of ethical issues. This protocol document describes the methodological approach for the CADTH components of the broader HTA. The methodological approach for the components Health Quality Ontario is conducting is described elsewhere.

A Qualitative Evidence Synthesis: Patients' and Health Care Providers' Perspectives and Experiences

A rapid qualitative review will be conducted, following an adapted process to produce a Rapid Response Summary with Critical Appraisal. The purpose of this review is to supplement a quantitative assessment of personal utility values that Health Quality Ontario will develop. Health Quality Ontario may also decide to use the preliminary findings of this rapid qualitative review to conduct direct patient engagement with Ontarians as a way of providing more contextual depth.

Research Questions

1. How have families, and their health care providers, seeking clarity on a person's unexplained developmental delays or multiple congenital anomalies, experienced engaging with the processes of whole exome and/or whole genome sequencing as a diagnostic tool? For example, among other things:
    - How have sequencing, and subsequent results, been presented by health care providers as an option for families and individuals seeking this clarity?
    - How have variable results (e.g., diagnostic, semi-diagnostic, uncertain significance, secondary findings) been received, interpreted, articulated, and acted upon by individuals and their families?
2. How have the varied discourses (e.g., clinical, policy, pop culture) surrounding whole exome and/or whole genome sequencing been articulated by families, and their health care providers, in light of these experiences? For example, among other things:

- How (if at all) might these varied discourses be drawn upon to articulate the expectations at play in regards to whether to proceed (or not) with sequencing?
- How (if at all) might these varied discourses be drawn upon to articulate the importance of receiving a diagnosis (or not) through sequencing?

Methods

As this review is being conducted through the Rapid Response Service, an unpublished topic refinement form will be used in place of a traditional protocol document. However, the research questions, as documented previously, and the selection criteria for this review, as outlined in Table 1, are included for reference. The final methodological approach will be reported within the Rapid Response publication, which will be posted on the CADTH website.

Table 1: Selection Criteria

Population(s)	Individuals living with unexplained developmental impairments (or those for whom a diagnosis has subsequently been achieved), as well as their families and primary care providers
Intervention(s)	Genome-wide sequencing: • whole exome sequencing • whole genome sequencing
Context/Setting	Use of whole exome and/or whole genome sequencing at various times in genetic investigations
Outcome(s)	Issues emerging from the literature that relate to descriptions of experiences engaging with genome-wide sequencing for the diagnosis of unexplained developmental delay. This may include, among other things, perspectives on the relevance or utility of testing, perspectives on access to testing, perspectives on the sorts of results sequencing provided or may provide, potential benefits and harms of the sequencing process, perspectives of how sequencing fits into the "diagnostic odyssey," and discussions of expectations of sequencing broadly speaking
Study Design(s)	Qualitative studies of any design

Ethical Issues Analysis

Study Design

A *de novo* ethical analysis will be conducted to identify and reflect upon key ethical concerns that should be considered when considering genome-wide sequencing for unexplained developmental impairment. Although other sections of this HTA will touch upon broad ethical concerns, the aim of this analysis is to make such issues explicit and to identify others that may be relevant to any decisions in this regard.

The issues raised in this section can go beyond narrowly defined ethical concerns to encompass broader legal, social, and cultural considerations, as well. Nevertheless, the primary emphasis here will be on ethical considerations rather than on legal and social issues.

Research Questions

There are two sets of questions to consider when employing genome-wide sequencing for unexplained developmental impairment:

- What are the major ethical issues raised by the use of genome-wide sequencing for clinical purposes (including whole exome and whole genome sequencing) compared with other diagnostic tests including combinations of genetic tests such as chromosomal microarray and gene panels for pediatric and adult populations with intellectual disability, developmental delay, congenital anomaly, multisystem involvement and/or multi-differential diagnosis, or rare disease otherwise not specified?
- How might these issues be addressed?

These questions can be considered as matters of systems-level (or population-level) ethics, which examines decisions that will affect large numbers of people, and in which outcomes and interests are considered in aggregate (organizational ethics, policy ethics, and public health ethics are all domains of systems-level ethics). For systems-level ethics, instead of asking, “Does this technology benefit the patient?” or “Does this technology disadvantage a vulnerable individual?” we ask, “Does this technology create overall benefit with minimized and proportional harms for the population?” and “Does this technology disadvantage marginalized groups?”

These questions can also be considered at the individual level, invoking individualistic considerations that are typically concerns of clinical ethics (rather than systems-level ethics). Within a clinical ethics paradigm, the ethics analysis considers matters of respect for persons, autonomy, dignity, harms/benefits, and fairness, from an individual perspective. These considerations inform recommendations for whether and how a technology can be implemented and delivered in a way that reflects these key values and principles. If the analysis determines that the technology cannot be implemented in a way that sufficiently lives up to these core values, this may influence the acceptability of the technology at the systems level.

Inquiry

Bioethical analysis requires a two-step approach to identifying potential issues. The first is a review of bioethics literature to identify existing ethical analyses of the technology. The second is a novel ethical analysis based on gaps identified in the ethics literature and the results of concurrent reviews. This may require selective searches to provide the basis in theoretical ethics, in applied ethical analyses of similar technologies, and in the evidence for the ethical analysis of emerging issues specific to genome-wide sequencing. By this approach, we identify and assess the relative importance and strength of the identified concerns and proposed solutions, identify and assess issues that have not yet come to the attention of the ethics researchers, and delineate ethical desiderata for possible solutions to the issues where such solutions have not yet been proposed.

Insofar as this process involves ethical concerns in applied ethics, typically the analysis will reflect on the specific details of community and patient perspectives, clinical utility, economic analysis, environmental impacts, and implementation considerations. The ethical review thus involves an iterative process whereby the analysis is responsive to results emerging from clinical, implementation, patients’ perspectives, and economic analyses.

Perspectives

The relevant perspectives that need to be considered in identifying and addressing the ethical issues associated with genome-wide sequencing include those of patients, family members or informal caregivers, patient organizations, health care providers, and health care insurers.

Review of the Bioethics Literature

A review of the empirical and normative bioethics literature will be conducted to identify literature relevant to the identification and analysis of the potential ethical issues related to the use of genome-wide sequencing for unexplained developmental impairment, as well as genome-wide sequencing more generally. We will search for articles, studies, and reports that explicitly and specifically raise ethical issues related to the central question of genome-wide sequencing, as well as literature not explicitly about ethical issues (for example, an empirical investigation of patients' attitudes about genetic testing and genome-wide sequencing specifically but that may point to potential ethical issues even if the participants and researchers did not formulate them as such).

Literature Search Methods

The search for literature identifying explicit ethical considerations will be performed by an information specialist using a search strategy peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[24] The search strategy is available on request.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid and Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be genome-wide sequencing and unexplained developmental impairment. The initial search will be comprised of a narrow review of genome-wide sequencing (WGS and WES) for intellectual disability, developmental delay, congenital anomalies, multisystem involvement and/or multi-differential diagnosis, and rare diseases otherwise not specified in adult and pediatric populations. This search will include articles that include ethics dimensions of the technologies for both clinical and research applications. If this search does not yield sufficient literature, the search will be broadened to include articles on genome-wide sequencing for any conditions (e.g., also cancer).

Search filters will be applied to limit retrieval to citations related to empirical and normative ethical considerations. Retrieval will not be limited by publication date but will be limited to the English language. The initial search will be completed in March 2019. Regular alerts will update the search until the publication of the final report.

Grey literature (literature that is not commercially published) will be identified by searching Canadian and major international health technology agencies, as well as via a focused Internet search. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate.

Literature Screening and Selection

The selection of relevant literature will proceed in two stages. In the first stage, the title and abstracts of citations will be screened for relevance independently by a single reviewer. Articles will be categorized as "retrieve" or "do not retrieve," according to the following criteria:

- provides normative analysis of an ethical issue arising from the use of genome-wide sequencing for clinical purposes (including WES and WGS) compared with other diagnostic tests including combinations of genetic tests such as chromosomal microarray, and gene panels for pediatric and adult populations with intellectual disability, developmental delay, congenital anomaly, multisystem involvement and/or multi-differential diagnosis, or rare disease otherwise not specified
- presents empirical research directly addressing an ethical issue arising in the use of genome-wide sequencing.

In the second stage, the full-text reports will be reviewed by a single reviewer with ethics expertise. Reports meeting the aforementioned criteria will be included in the analysis, and reports that do not meet these criteria will be excluded from the analysis.

Data Extraction and/or Abstraction Strategy

The bibliographic details for each report (e.g., author, publication date, journal), the potential ethical issues raised, and the report's conclusions (issues identified, values at stake identified through normative analysis, and solutions proposed, and their normative justification, if presented) may be summarized in a table if this is deemed relevant and useful.

Analysis

The ethical issues identified, values described, and solutions proposed in the literature will at this stage be evaluated using the methods of ethical (applied philosophical) analysis, which includes applying standards of logical consistency and rigour in argumentation, particularly where specific implications are identified and specific solutions advocated; responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; adequacy to the context for which the technology is being considered; and the representation of perspectives from diverse relevant communities, particularly attending to the possibility of the neglect of marginalized and vulnerable populations.

The proposed analysis will start with the key values and principles which emerge from the literature review. This will likely include the consideration of core clinical ethics principles (beneficence and non-maleficence, privacy, etc.), as well as key systems-level concerns including medicalization, equity, and vulnerability, paying special attention to the perspectives of those who may engage with WGS, who may already be members of marginalized populations.

To ensure that the analysis is as comprehensive as possible, a series of questions developed by Hoffman (Harmonization of ethics in health technology assessment: a revision of the Socratic approach)[25] will be used to engage with the literature. These questions begin with the context of morally relevant issues related to the technology and the patient group; the ethical, social, cultural, legal, and religious challenges related to the health technology; the moral challenges, with structural changes related to the health technology; the moral issues related to the stakeholders; and the ethical commitments of the HTA process itself.

Summarizing and Presenting Results

The reporting of ethical issues will follow the key values identified or issues being explored and will be determined by the values and issues that are identified. For example, the results may be summarized according to a principlist framework (issues concerned with autonomy, beneficence, non-maleficence, and justice) or by categorizing moral concerns as micro-, meso-, and macro-level issues. Regardless of the framework selected, the implications of the choice of framework on how the findings are presented and interpreted will be described. In addition, it will be noted where the report undertakes analysis that is not derived from the peer-reviewed literature. It may also be appropriate to summarize the bibliographic details for each report (e.g., author, publication date, journal), the potential ethical issues raised, and the report's conclusions, as well as other information. The relevance and appropriateness of providing this summary will be determined once the analysis is completed.

Ethical analysis assists in social and policy decision-making but is not itself the site of legitimate social decision-making, which requires the consultation and deliberation on the part of relevant stakeholders in a given context. Decisions will also be sensitive to emerging empirical evidence. Furthermore, the ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, for example, are determined by facts about how health care services are arranged and provided.

Given these features of ethical decision-making, results of the ethics review will be presented in a way that helps decision-makers better understand the ethical implications of the decisions and recommendations they come to. For example, a number of contextualizing questions may be developed based on the identified issues so that decision-makers can assess localized impact, and proposed solutions will be analyzed to indicate the relevant ethical trade-offs at stake and mitigation strategies that could be employed to manage these trade-offs.

Opportunities for Stakeholder Feedback

CADTH will coordinate the posting of drafts for public stakeholder feedback with Health Quality Ontario. Stakeholders will be given the opportunity to provide feedback on the draft reports and recommendations. Unpublished data identified as part of the feedback process may only be included if the source of the data is in the public domain.

Protocol Amendments

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data, according to the amendments.

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