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Genome-Wide Sequencing: Ethical Considerations

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No conflicts of interest were declared by the author or reviewers of this report.

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Abbreviations

CMA	chromosomal microarray
GWS	genome-wide sequencing
HTA	health technology assessment
VUS	variant of uncertain significance
WES	whole exome sequencing
WGS	whole genome sequencing

Executive Summary

What Ethical Considerations Arise With GWS?

Genome-wide sequencing (GWS) is subject to many of the same ethical concerns as other genetic tests including considerations of respecting individual autonomy through consent processes, balancing harms and benefits with attention to stigmatization, protecting confidentiality while considering how to protect individuals related to the individual, and how to manage incidental findings. GWS generates some novel ethical concerns however, due to a high volume of incidental findings and the substantial uncertainty inherent to the technology and the results. Both of these factors can make it difficult to adequately support patients and families through GWS, thus raising the risk of creating harms for the patients the technology intends to help.

Should Genome-Wide Sequencing Be Funded?

GWS has been shown to have the potential to offer a balance of benefits over harms to a subset of individuals with unexplained developmental disabilities and multiple congenital abnormalities, and to their families. It may also reduce the overall costs of genetic testing and so appears to live up to the duties of conferring benefit at a population level and steward scarce resources. Realizing these benefits and reduced costs will depend on how GWS is organized and delivered, and careful attention to this process will be critical to ensuring that funding this technology remains an ethically supportable option.

How Should Genome-Wide Sequencing Be Organized and Delivered?

The promise of benefits from GWS is continuously shifting, which contributes to substantial uncertainty with its use. If GWS is funded, attention will need to be focused on the organization and delivery of services to ensure they live up to core ethical duties of maximizing benefits over harms, both for individuals and the population; preserving confidentiality; responding to vulnerability; and promoting fairness and justice, particularly to do with access to services. Duties to distribute benefits and burdens fairly require that we are attentive to the accessibility of testing and diagnostic services. Stakeholders have noted that it will be important to identify the subset of patients for whom this testing will be most useful to avoid crowding out access with patients for whom the test offers little promise. Detailed and skilled counselling and informed consent processes will be important to ensure that patients and families are prepared and have realistic expectations about GWS. Training will be necessary at all levels of care to ensure that health care providers appropriately refer patients to GWS and can accurately interpret the results.

Three key issues deserve special attention: the management of incidental findings, the effects of uncertainty, and the implication for professional roles.

- Incidental findings are results that are unrelated to the original purpose of the test but may be relevant to patients and/or their genetically related family members. Patients (or in the case of those who lack capacity, their surrogate decision-makers) and their families should be informed about the potential for incidental findings and given choices regarding whether they wish to be informed if any arise. If it is the patient's or family's informed decision not to receive certain types of information, it is ethically appropriate for genetic services not to disclose these findings, with some limitations. It can be ethically justified to require the mandatory disclosure of incidental findings to parents or guardians in the case of children if the findings reveal substantial and immediate potential harms that may be mitigated through health interventions.

- The rapid evolution of GWS has generated substantial excitement about its promise. It also creates a certain amount of uncertainty about whether the test would ultimately be beneficial, which that can make it difficult to determine specifically what its promise is and for whom. A humble and honest approach in testing, therefore, is appropriate to ensure that patients and families are prepared and have realistic expectations about what GWS may provide medically, socially, and emotionally.
- The funding and widespread implementation of GWS will have ethical implications for the roles and duties of various health professionals. If GWS is made available through established genetic services, then it is likely to benefit from the professionals within those services who are already familiar with many of the genetics-related issues that GWS will bring. If GWS is implemented in a way that allows primary care professionals to seek GWS directly for their patients, there is likely to be less existing expertise in determining the appropriate use of GWS, thus challenging the assurance of robust informed consent and management of test results including variants of uncertain significance and incidental findings. If the latter approach is taken, it will be important to ensure that the health care professionals involved with GWS have the appropriate tools and training, and it may be important to identify the subset of patients for whom testing will be most useful to avoid crowding out access with patients for whom the test offers little promise.

Context and Policy Issues

About one-half of people living with congenital anomalies have not had a specific cause or diagnosis identified based on their clinical presentation or examination of environmental causes. Such individuals are given a label of "unexplained developmental delay" and it is not uncommon for them to be subjected to multiple diagnostic tests venturing on what some refer to as the "diagnostic odyssey." Genetic sequencing has the potential to alleviate these diagnostic odysseys and provide definitive diagnoses otherwise undetectable by clinical history, physical examination, and biochemical or metabolic tests, or to do so sooner than current practice.

Next-generation sequencing technologies — like chromosomal microarray (CMA) and genome-wide sequencing (GWS) — require patients to undergo a standard blood draw that is sent off to a laboratory for analysis. The sequencing, analysis, and interpretation of these technologies, however, is situated within complex bioclinical collectives[1] made up of highly specialized professionals such as molecular analysts, bioinformaticians, and laboratory geneticists. While the sequencing itself is automated, and algorithms do exist to help identify notable mutations, these collectives must collaboratively interpret sequencing results to connect phenotype to genotype and establish whether identified variants should be considered pathogenic.[2] For technologies like GWS and CMA, pathogenicity is labelled along a scale from pathogenic to benign. For example, the American College of Medical Genetics has developed and standardized five descriptive reporting categories: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign. Interpretations are based on known phenotypic associations, as documented in open access databases (e.g., Online Mendelian Inheritance in Man, Human Gene Mutation Database), as well as group discussions around natural history and clinical presentation.[2]

Unlike single gene or gene panel sequencing methods that focus on single or small sets of genetic material information, next-generation sequencing reads millions of fragments of genetic information in parallel. This makes the sequencing process substantially faster, but it also requires those within the bioclinical collective to be broadly familiar with potential genetic variations.[2] This also has the effect of increasing the amounts of variants returned that may be causally relevant to the person's condition (i.e., VUS) but cannot be determined with certainty.

Test results and subsequent interpretations of pathogenicity confirmed, they are then returned to the clinic and shared with patients and their families, who necessarily find ways of incorporating them into their lived worlds.

Policy Question

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

Objective

CADTH collaborated with Health Quality Ontario to conduct a health technology assessment (HTA) on the topic of GWS. Specifically, this report aims to inform the policy question by providing an analysis of related ethical considerations.

Research Questions

There are two sets of questions to consider when employing GWS for unexplained developmental disabilities and multiple congenital anomalies:

1. What are the major ethical issues raised by the use of genome-wide sequencing for clinical purposes (including whole exome sequencing 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?
2. How might these issues be addressed?

Study Design

A *de novo* ethical analysis was conducted to identify and reflect upon key ethical concerns that should be contemplated when considering GWS (including whole exome sequencing and whole genome sequencing) for unexplained developmental disabilities and multiple congenital anomalies. Although other sections of the HTA, reported elsewhere,[3] 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.

Background

Ethics is the inquiry into the goodness or rightness in life; it examines questions about what we owe to each other and what it means to be a good person. Applied ethics uses ethical or moral theory (ethics and morals are used interchangeably in this analysis) to find answers to these questions for particular topics and contexts. Topics or questions where important values are clearly at stake for individuals or populations are called ethical issues. The goal of an applied ethics inquiry is to identify the relevant values and principles, and determine the implications of these principles and values, for a particular issue or question.

HTA is the evaluation of new technologies or new applications of existing technologies to determine whether they should be implemented (and sometimes publicly funded) within a health care system. HTA is fundamentally value-laden and proceeds with the following implicit ones:

- the technology should achieve the goal it set out to achieve
- the technology should achieve that goal without creating more harm than good
- the financial requirement to adopt and implement the technology should not be disproportionate to its benefit
- adopting the technology should not pose serious threats to human integrity and dignity.

In addition, there are two broad normative questions that are relevant to most HTAs:

1. Should the technology be endorsed or made widely available?
2. If yes, how should the technology be made available?

Both of these questions are matters of systems-level or population-level ethics, which examine questions that will affect a large number 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?” and “Does this technology disadvantage

vulnerable individuals?," we ask, "Does this technology create overall benefit for the population?" and "Does this technology disadvantage marginalized groups?" Questions of individual autonomy are of lesser concern when using this approach; however, if a technology were to present broad challenges to individual choice within a relevant population, this would be reason to consider seriously whether it would be ethically justifiable to endorse or implement the technology universally.

The determination that a technology should not be implemented may be made for several reasons:

- The technology offers little to no evidence of benefit at the population level.
- The technology does offer benefit at the population level, but the degree of benefit is disproportionate to the cost.
- The technology presents substantial issues of respect for persons affected by the technology, and these issues cannot be mitigated by careful implementation. Such issues include systematic affronts to dignity, autonomy, and personhood, and the oppression of particular groups, especially those who are already vulnerable or who may be made vulnerable as a result of the technology.

Returning to the broad normative questions, if the answer to the first is "yes," then the second must be considered. This requires consideration of the nature of the technology from the individual perspective, invoking an individualist or bedside ethics approach (sometimes referred to as "clinical ethics"). Closer attention must be paid to principles of respect, benefit, autonomy, dignity, and fairness from the individual perspective to uncover how the technology can be implemented and used in a way that lives up to these key principles. If analysis determines that the technology cannot be implemented in a way that sufficiently lives up to these principles, it may cause the first question to be reconsidered.

Inquiry

Ethics analysis requires a two-step approach. The first is a review of the ethics, clinical, and public health literatures to identify existing ethical analyses of the technology. The second is a *de novo* ethical analysis based on gaps identified in the ethics literature and the results of concurrent analyses being conducted as part of the broader HTA. Through 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 ethics researchers, and delineate ethical desiderata for possible solutions to the issues where such solutions have not yet been proposed.

Review of the Bioethics Literature

A review of the empirical and normative bioethics literature was conducted to identify literature relevant to the identification and analysis of the potential ethical issues related to the use of GWS for unexplained developmental disabilities and multiple congenital anomalies, as well as GWS more generally. We searched for articles, studies, and reports that explicitly and specifically raise ethical issues related to the central question of GWS, as well as literature not explicitly about ethical issues — for example, an empirical investigation of patients' attitudes about genetic testing and GWS 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 was 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).[4] The search strategy is available on request.

Published literature was 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 was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were GWS and unexplained developmental impairment.

Search filters were applied to limit retrieval to citations related to empirical and normative ethical considerations. Retrieval was not limited by publication date, but was limited to the English language. The initial search was completed in March 22, 2019. Regular alerts updated the search until the publication of the final report.

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

Literature Screening and Selection

Literature was included if it explicitly identified ethical issues regarding GWS or if it discussed ethical issues relating to analogous technologies. Additional articles were included based on the judgment of the report author and suggestions from reviewers.

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

- provides normative analysis of an ethical issue arising from the use of GWS for clinical purposes (including whole exome sequencing [WES] and whole genome sequencing [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 from the use of GWS.

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

Results and Analysis

For this analysis, GWS is understood to entail a combination of up to three elements:

- rapid testing for multiple known disease variants
- testing for as yet unknown variants that clinicians can use for personalized diagnosis and management

- information gathering for databases of possible variants for future investigation and validation of determinations of diagnostic significance.

The ethical considerations that emerged in the literature review can be organized according to five key ethical principles or duties. These are: the duty to create benefits and minimize harms for patients, families, and others; the duty to respect individual autonomy and personhood; the duty to maintain confidentiality; the duty to promote fairness and justice; and, finally, the duty to respond to vulnerable populations. The following section discusses the ethical significance of these principles to GWS. For simplicity, the term "patient" (rather than "proband" or "participant") is used throughout this document to refer to the person with unexplained delays or anomalies who may undergo GWS.

Of note, many of the issues that are highlighted in this section are not unique to GWS. Ethical concerns with privacy and confidentiality, stigmatization, incidental findings, and implications for individuals genetically related to the patient emerged with previous genetic technologies and have been widely discussed in the literature. GWS brings novel ethical concerns, however, to do with informed consent, the vulnerability of the target population, and equity considerations particularly to do with representation in reference data sets. GWS is also uniquely likely to generate a much higher volume of incidental findings and VUS as compared with other genetic technologies, both of which can have ethical implications for its use. It is these novel issues that should be considered in deciding whether GWS is ready for use in regular clinical practice or whether it should remain within the realm of research for a longer period of time.

The relevance of these novel ethical considerations will depend on how GWS is implemented. If GWS is made available through existing mechanisms of genetics referral and counselling, then it will be under the purview of geneticists and genetic counsellors with the expertise and experience to manage many of the issues raised by GWS. If GWS is made available through primary care providers (as a starting point, with referrals to others), then at least some of the health care providers involved will be less familiar with the technology and its necessary skills and expertise, which will likely have an impact on patient access, consent procedures, and possible harms to patients and relatives. If GWS is implemented through primary care mechanisms, substantial education for professionals will be necessary.

Finally, ethics is a normative discipline — it focuses on how things ought to be rather than how they are (keeping in mind that good facts are crucially important for good ethics). The sections that follow will discuss both the ethics dimensions of GWS and its delivery, as well as strategies reported in the literature, which may enable providers to live up to key ethical obligations. These strategies may not be realistic or feasible in every context; however, they nonetheless are useful, as they signal what can be worked toward to achieve optimized ethical implementation and delivery of GWS, if it is funded.

Duties to Create Benefit (Beneficence) and Minimize Harms (Non-Maleficence)

The principles of beneficence and non-maleficence (i.e., the duties to create benefits and minimize harms) sit at the core of health ethics and are most familiarly part of the "four principles" approach to bioethics, alongside the principles of autonomy and justice.[5] They are typically considered within the context of a health care provider's duty to their patients; however, the principles also apply more broadly to consider duties to family members, and to larger populations or society more generally. Considering the potential effects of a technology to individuals aside from the patient is especially appropriate within the context of

genomics, as the human genome is shared among all humans and genetic information about individual patients will substantially overlap with the genetic information of biologically related family and within highly genetically related communities.

The duties to create benefits and minimize harms apply in the clinical context (i.e., where medical care is provided) and in research, although in a research context the ethics are more complex, as research isn't intended primarily for the benefit of the research participant. Rather, research — especially health and genetic research — is typically pursued with the intention of generating knowledge that may be beneficial to future patients or populations of patients. Nevertheless, research studies must be developed with the impact on individual research participants in mind, especially when participants are vulnerable in some way, as is the case with individuals with unexplained developmental disabilities and multiple congenital anomalies. Further, the ethics dimensions of research in GWS are relevant to this HTA because patients currently get access to WGS and to a lesser degree WES through research (at least in Canada), as WGS in particular is not widely available in clinical contexts.

The following sections outline duties to create benefits and minimize harms to patients, to family (specifically, genetically related individuals), and to populations more broadly.

Duty to Benefit the Patient

GWS (which includes WES and WGS) for people with unexplained developmental disabilities and multiple congenital anomalies is generally taken to be a promising process that has the potential to offer benefit. Patients or their surrogate decision-makers (often their parents) will choose GWS, if offered, with the hope that it will yield a diagnosis that can provide a cause for the patient's presentation. It is often hoped that a diagnosis will yield a more informed prognosis and the potential for active therapy or medical management that might ultimately improve the patient's condition.[6-10] These benefits are often described in terms of "clinical utility," which in this HTA includes active medical management (e.g., change to medications, procedures, or treatment) and monitoring and long-term clinical management (e.g., additional testing, change in surveillance, referrals, participation in clinical trials, involvement in social services, lifestyle change).

If GWS yields a diagnosis that does not offer any further medical management, this may still be viewed by the patient as beneficial because the diagnosis may signal the end of a "diagnostic odyssey" — the series of tests and clinic visits that a patient endures, often over several years, to try to determine the underlying cause of delays and anomalies.[6,8-11] The end of this diagnostic process may relieve stress for the patient and their family by resolving any uncertainty they may be experiencing living without a diagnosis, by ending the felt need to continue to find a diagnosis, or by determining that certain genetic disorders are unlikely. [7]

Some authors have noted that, while a diagnosis can spell the end of a diagnostic odyssey, it could also mark the beginning of a (new) "therapeutic odyssey" if the diagnosis is amenable to further treatment or monitoring.[8] Clinic visits for testing could be replaced by visits for treatment or ongoing monitoring, which bring their own stresses and burdens for the patient and their caregivers. If ongoing monitoring involves invasive testing (e.g., blood tests, colonoscopies), new questions arise about the appropriateness of this path, especially if a patient's cognitive impairments prevent them from understanding the purpose of such possibly uncomfortable intervention.[12]

A diagnosis, whether or not it leads to changes in medical management, may also be beneficial to some patients and family members because it could allow them to make reproductive decisions.[7] Because the proportion of patients within the population of study for

this HTA who may be considering reproduction may be small, for some conditions, this benefit is more likely to be available to related family members, so is discussed in a subsequent section.

A diagnosis through GWS may also offer a series of non-medical benefits. In Ontario, specialized services and supports are provided to individuals based on presenting delays or anomalies rather than diagnostic labels; however, a specific diagnosis could enable patients and their families easier access to such services and social programs.[10] Further, a diagnosis may enable patients to find and interact with others with the same or similar diagnoses, which may be valuable.[12]

The extent to which GWS is likely to provide many of these benefits to any one patient is not clear. As outlined in the clinical evidence review,[13] approximately 37% of patients who undergo GWS will receive a diagnosis, and many rare diseases do not currently have approved treatment.[8] This means that for most patients the test offers no further certainty. Offering GWS to patients within the population of interest may live up to our duties to benefit patients if we understand benefit to include not only determining useful diagnoses or helpful clinical management, but also the potential to retrieve these benefits with the understanding that they are not guaranteed for any individual patient.

Duty to Minimize Harms to the Patient

In addition to having the potential to offer benefits to the patient, GWS can also prevent or minimize the patient's exposure to harms. Clinically, a diagnosis may put an end to ineffective treatments that may exacerbate symptoms or come with their own harmful side effects, ultimately reducing patient suffering.[11,14] In some cases (typically in neonatal contexts), a diagnosis may indicate the futility of ongoing treatment and may assist a shift toward palliative or comfort-oriented measures.[9,11,14] While GWS is not tightly linked to palliative care in the literature or in practice, it is important to be aware how a portrayal of GWS as a tool for determining whether a shift to palliative goals is appropriate could be, as pointed out by some stakeholders, construed as eugenics. It is also possible that GWS will yield incidental findings; for example, susceptibility for chronic disease or malignancies, which could be addressed and result in decreased morbidity and mortality.[12] A more detailed discussion of incidental findings is found in the discussion in the Key Issues section of this report.

It is possible for GWS to expose patients to harms. If GWS yields a diagnosis, some have wondered if this label may actually interfere with the diagnosed patient's ability to get certain types of medical care in the future. Deem [15] notes that persons with disabilities are sometimes taken to be inappropriate or poor candidates for particular medical interventions; for example, organ transplantation. Decision-makers who control access to limited organs for transplant generally attempt to ensure those decisions are based on objective criteria; however, they often consider criteria including the anticipated quality of life of the patient, which disability advocates have raised may be based on false assumptions for persons living with disabilities, as they rarely take into account the perspectives and experiences of the patients (or their caregivers) living with the types of conditions likely to be diagnosed by GWS.[15]

If GWS yields a genetic variant that indicates the patient may develop a medical condition in the future, the patient may then be subject to invasive or harmful medical procedures that may not actually yield any benefits.[16] Further, for patients with sufficient cognitive capacity, GWS may present emotional or psychological distress when the expectations set by GWS (i.e., that it yields a diagnosis or provides any type of clinical utility) are not met.[16] Because

many individuals expect that testing will yield further valuable information, for some, and especially those among the approximately 63%[13] who do not receive any diagnosis, there may be substantial disappointment when it does not. There may also be disappointment even for those who do receive a diagnosis, as this may come with an unmet expectation that a diagnosis brings a change in management that could lead to material improvement for the patient. Some authors have noted that it is not surprising that diagnoses, especially for rare diseases, tend not to come with potential therapies, as the current focus of GWS is to identify genes to target for prevention and treatment, with the research to develop treatments coming later.[8] It is important that all those involved in GWS (patients, family members, etc.) are supported in having realistic expectations, which is discussed in more detail in the discussion on autonomy and informed consent in this report.

It is also possible that the information yielded by GWS, whether as a diagnosis or identification of a VUS, will make the patient vulnerable to stigma and discrimination.[16] This may entail social discrimination of some kind, although individuals with unexplained developmental disabilities and multiple congenital anomalies may already be subject to such discrimination due to their symptoms and phenotype. Many authors have proposed that GWS could lead to patients being vulnerable to discrimination by insurers and employers, [16-18] although others have pointed out the number of cases of actual discrimination by insurers is small and the concern for discrimination has been overstated.[19] Further, in 2017 Canada passed the *Genetic Non-Discrimination Act* that prohibits employers and companies from requiring genetic information as a condition of employment or services.[20] The Act forbids denying services to individuals if they decline genetic testing and also prohibits the collection, use, and disclosure of an individuals' genetic test results without their written consent. The Act, in effect, makes it illegal for insurance providers to require the results of any genetic testing. With these protections, the risk of loss of insurance and related discrimination as a result of GWS should be minimal. Experts who provided feedback on this analysis and report expressed concern that the Act does not go far enough, however, to protect individuals. Also, Quebec has launched a court challenge related to the jurisdiction of the Act, which may put the status of the Act in question.

The ethical considerations raised here suggest there is potential that GWS could both prevent and create harms for patients who undergo GWS. Whether or not duties to protect patients from harm are lived up to will specifically depend on how the technology is implemented and used.

Duty to Benefit Family

When patients undergo GWS, it is common for their biologically related parents to be tested as well, so that genetic information is generated for three individuals rather than only the patient. Even in cases where only the patient is tested, genetic testing often reveals information that can be beneficial for related family members,[17] including physiological benefits, as well as psychosocial benefits.

Physiologically, GWS of one family member can reveal traits present in biologic relatives that could be addressed or ameliorated through subsequent monitoring or clinical interventions.[17] Genetic information obtained through GWS may also assist family members in making future reproductive decisions if they wish to avoid passing a genetic variant to future offspring.[17] Psychologically, a diagnosis for the patient may relieve distress for family members, especially on the part of parents who are typically burdened by not knowing the cause of their child's anomalies.[21] As previously discussed, a diagnosis may mark the end of the diagnostic odyssey, which for family members can be practically and psychologically burdensome. In some cases, it is proposed that a diagnosis may alleviate guilt that is

sometimes experienced by parents, especially biological mothers who may blame themselves for causing their child's difficulties.[9] A diagnosis may also yield social benefits for parents, as it can enable parents to find others who are caring for individuals with the same diagnosis, which in turn could provide social and emotional supports, a sense of connection with these families, and possibly also yield more information about resources and strategies to aid in caring for the diagnosed individual.

As GWS may offer benefits for relatives and caregivers of patients with unexplained delays and anomalies, it has the potential to live up to duties to create benefit for families.

Duty to Minimize Harms to Family

GWS of patients raises questions of potential physiological harms to family members, both as genetic relatives and as caregivers. For related family members, GWS of the patient could yield information relevant to their own health and well-being. Genetic information relevant to family members may also emerge if family members are tested directly, as often when children undergo GWS parents are tested, as well. Either way, such testing may reveal genetic variants in family members that could indicate their increased risk of developing health conditions in the future. If health care professionals do not or cannot notify family members of such risk, they could be perceived as failing to live up to their duty to prevent harms to family.[16] This circumstance is complicated if a patient wishes not to disclose their genetic information to family members even when it contains information about risk relevant to those family members.[7] There is perhaps a low likelihood of this situation in the context of the population under consideration, as many patients will not have the cognitive capacity to make their own health care decisions. As a result, a surrogate decision-maker (often parents or other family members) would be involved and would be informed of any information about familial genetic risk. Even in such circumstances, questions remain about how to manage personal genetic information that has implications for the health and well-being of others. This topic is discussed in more detail in the Duty to Protect Confidentiality section.

GWS may also raise potential psychosocial harms to a patient's family members. Many of these have been discussed in the context of potential harms to patients, including the stress of uncertain findings, unmet or unrealistic expectations. There may be additional stress for parents, however, if GWS reveals an incidental finding suggesting that their child is vulnerable to adult-onset conditions, especially if these are unrelated to the reason for sequencing or are not clinically actionable.[16] It is also possible that parents learn of misattributed parentage through GWS, which, if revealed, could cause substantial distress to everyone involved.[22] In this case, there could be threats to the integrity of the family structure, including disruptions in parent-child bonding and self-partner blame.[23]

Given these concerns, there is some potential that GWS could both prevent and create harms for relatives and caregivers of patients who undergo GWS. Whether or not duties to protect families from harm are lived up to will specifically depend on how the technology is implemented and used.

Duties to Create Benefit and Minimize Harms to Others

For systems-level decisions like the one considered in this HTA (i.e., whether or not to fund GWS), decision-makers also have duties to consider how the decision may affect others, including specific communities or subgroups, the population as a whole, or future generations.

Whether or not to make GWS more widely available (as would occur if a decision were made to publicly fund GWS) can have implications beyond the specific individuals who or populations that may presently be affected by the technology.[16] A decision to fund GWS could draw shared public resources away from other possibly worthy endeavours, and specifically in the case of GWS could have impacts on norms around parenting, public attitudes about disability, and the rights of children.[16]

In general, there is optimism about the promise of GWS to yield benefit to the population as a whole, with the potential to prevent and appropriately treat disease.[24] This may be of particular interest in settings (such as Ontario) where there is publicly funded health care[25] and so a shared interest in identifying and treating disease efficiently. Increased GWS among those living with unexplained developmental disabilities and multiple congenital abnormalities where sequencing data are added to genetic databases could lead to further benefits for others who have similar presentations in the form of improved diagnosis and prognostication.[12] There may also be a sense of solidarity among patients and families that leads them to choose to make a patient's genotype and phenotype data available to assist others in arriving at a diagnosis.[6] Within the Ontario context, there is anecdotal evidence indicating that patients and families are generally motivated to share their data if doing so can help others going through similar challenges (Dr. Kym Boycott, Clinical Geneticist, Department of Genetics, CHEO–Children's Hospital of Eastern Ontario; Professor, Department of Pediatrics, Faculty of Medicine, University of Ottawa, Ottawa, ON: personal communication, 2019 Apr 18). Of note, this willingness to share data has most often been observed in a research context; and, it is not clear whether there would be similar willingness among families receiving care in a clinical context.

In spite of the general optimism about the positive potential for GWS, disability rights advocates have expressed some reservations about its use, particularly in the context of symptomatic neonates.[15] In general, advocates from this group are concerned that genetic technologies may reinforce the stigmatization and discrimination of persons living with disabilities, both in social and in medical contexts.

Several authors[9,11,14] have noted that GWS may offer benefits to symptomatic neonates and their families by allowing for the early identification of serious and lethal genetic conditions, thus enabling the neonate to avoid protracted periods of ineffective treatment by shifting to a palliative course. While GWS is not tightly linked to palliative care in the literature or in practice, it is important to be aware how a portrayal of GWS as a tool for determining whether a shift to palliative goals is appropriate could be — as pointed out by some experts who provided feedback on this review and analysis — construed as eugenics, and negatively affect social attitudes toward disability.[15] It is important, then, that GWS is portrayed neutrally as a tool for clinical management rather than a precursor to any particular course of clinical action. This concern is likely less acute for older individuals with congenital anomalies whose survival does not depend on ongoing life-sustaining treatment.

The ethical obligations to create benefits and minimize harms to patients and affected others apply to individual clinicians as well as those making broad policy decisions about how to organize and deliver health care. For policy decisions, such as whether or not to fund a technology, it is appropriate to consider how the technology may affect the well-being of the population as a whole, as well as to consider how the technology may affect individuals. If a technology appears likely to create a net harm to the population, either through directly harming individuals or by drawing away resources from beneficial treatments, then it may be ethically appropriate to choose not to fund the technology. If the technology is not anticipated to create a net harm for the population but is likely to present net harms to

individual patients or families, then it may be ethically appropriate not to fund the technology. In the case of GWS, it appears to offer a net benefit to the population of Ontario, as it has the potential to lead to more efficient resource use provided GWS enables patients and families to avoid or shorten their diagnostic odyssey (see the economic analysis for more details),[13] offers clinical utility to a meaningful proportion of those who are tested (see the clinical evidence review),[13] and may reduce psychosocial harms (in the form of stress and uncertainty) for patients and families living with unexplained development disabilities and congenital anomalies (see the review of patients' perspectives and experiences).[3]

Even if GWS is likely to offer net benefits at a population level, this discussion suggests that there is both potential to live up to and fail to deliver on the duties to promote benefit and minimize harms to individual patients, their relatives, and caregivers. Whether or not these principles are lived up to will specifically depend on how GWS is implemented and delivered.

Duty to Respect Autonomy and Personhood

The duty to respect autonomy and personhood arises from a central principle in Western culture that values the authority of the individual to determine what happens to their body and in their lives.[26] This principle generally overrides a health care provider's perspective on what is best for the patient. If a patient can demonstrate they are capable and understand the decision they are making, their autonomous choice ought to be respected, regardless of the consequences.[26] The authority to make decisions can be exercised directly by a person making decisions for themselves or indirectly by a surrogate making a decision on behalf of another.[17]

In medical contexts, the significance of this duty is most clearly enshrined in informed consent processes that are intended to enable patients, or their surrogates, to accept or decline medical interventions. The process of obtaining informed consent is meant to ensure that people are not coerced into particular courses of action by others. It is premised on the "essential psychological fact" [27](page 17) that human beings have differing perspectives, values, and wishes about their lives, and so will have different, yet totally reasonable, responses to their medical options.[27] Respecting individual choices does not require that all theoretically or technically possible services are provided at the request of the patient;[17] rather, it requires that a qualified health care provider put forth a range of potential options that may meet a patient's needs, and to respect the choice the patient or surrogate makes among those options, including the option not to proceed with an intervention at all.

This duty not only requires that one respect an individual's wishes in a decision-making process, which tends to be the focus of informed consent procedures, but more broadly to recognize the humanity of the whole person in every engagement. This duty also extends to acknowledging and appropriately responding to various types of cultural diversity. These three dimensions are subsequently discussed within the context of GWS.

Informed Consent

As with other medical tests, the purpose of seeking informed consent for GWS is to help ensure that the decision to undergo the test, either for oneself or for an incapable other, is made in an informed and uncoerced fashion: that decision-makers feel capable of deciding not to proceed with testing even if health care providers recommend it, or they feel free to change their minds.[16,17] It means that the person making the decision, either for themselves or someone else, understands the risks, benefits, and discomforts of the procedure being offered and are also aware of any alternatives, including the option not to proceed with any intervention or test.[17,28]

Providing informed consent is not simply a matter of signing a form; rather, done well, it is a process that unfolds over several conversations within the context of a therapeutic relationship with a health care provider so that the decision-maker understands the nature of the decisions they are making and their authority within these decisions.[29] A decision is more likely to be adhered to by the patient or decision-maker if it is made in a collaborative manner that supports patients and families to have a basic, but accurate, understanding of the nature of their condition and the treatment options.[17] This requires, then, that health care providers have sufficient knowledge of the medical intervention being offered so they can adequately and accurately outline the harms, benefits, and alternatives to treatment to patients in a way that the patient can best understand.[29]

GWS can look different for different patients. Some patients may wish to be informed about only variants of known significance, whereas others may wish to know about VUS, as well. Some patients may wish to contribute their genetic data to databases, whereas others may not. Each of these decisions is very specific to patients (and likely their families) and requires a careful and skilled informed consent process. One study estimated that a robust consent process for GWS takes between six and eight hours of a clinician's or genetic counsellor's time,[30] although it is unclear how reflective that is of best practice. How GWS will be implemented may have consequences from the quality of informed consent procedures. If GWS is provided through referrals to established genetic services, where experienced geneticists and genetic counsellors lead the patient through the informed consent process, then the consent may be more likely to be done well, as these health care providers already have much of the necessary knowledge and skill. If GWS is implemented in such a way that primary care providers or others typically lacking experience in genetic testing lead the consent process, then the consent process may be less robust, especially if there is no concomitant effort to provide accessible education to health care providers.

Many authors recommend that pretest counselling from a qualified medical professional be available to any patient considering GWS.[17,30-33] During this counselling with patients or their surrogates, conversation should help to establish realistic expectations through discussions of possible outcomes of the tests, including: the possibility that results will be ambiguous or conflicting;[17,32] the potential harms and benefits of the testing both for the patient and for family members;[31] how privacy and confidentiality will be managed;[32] and, the possibility of tests revealing incidental findings,[7,11] including the possibility that they could reveal non-paternity, unacknowledged adoption, and other non-biological relationships.[17] Patients or their surrogates will need to make decisions about whether they wish to be informed of any incidental findings, including information about carrier status for an autosomal recessive disease (a condition that may have implications for decisions for the patient or family members).[34] Patients may also wish to discuss whether and how they may wish to share results with other genetically related family members and whether their results may be included in research or databases.[35] The matter of incidental findings will be discussed subsequently in greater detail.

Many patients with unexplained developmental disabilities and multiple congenital anomalies will not have the full capacity to make medical decisions for themselves, either because they are children with developing capacity or they have limited cognition because of their anomalies.[31] It is ethically appropriate for those with limited capacity to have the support of surrogate decision-makers; however, diminished capacity does not mean that patients should be excluded from decisions altogether. Rather, patients with diminished capacity should be included in decisions to the extent that they are able, which is facilitated when health care providers share information at a level commensurate with the patient's level of capacity.[12] It is also ethically appropriate for minors without cognitive limitations to be

involved according to their development and maturity, and those with sufficient maturity to be accorded full decision-making authority.[17]

As much as respecting autonomy entails that individuals (or, if they are incapable, their surrogate decision-makers) have full and accurate information relevant to the decisions they face, there is a commensurate duty to respect individuals wishes not to find some or all of their genetic information. This is described as the "right not to know." Usually, this right is exercised by an individual choosing not to be tested; however, some individuals wish to be tested but only wish to be told a subset of the information yielded by the test.[17] In general, these wishes about which information patients or surrogates would like to receive, including choosing not to be tested at all,[36] should be honoured provided the possible consequences of not knowing certain information are understood.[7] Some authors argue that, in certain cases, a wish not to know should not be honoured, particularly if a surrogate decision-maker is choosing not to learn of results on behalf of another person (particularly a child) where these results are actionable — that is, where some steps may be taken to improve the health and well-being of that person should the results become known.[17,26]

There is a particular concern that within the context of genomics we are drifting away from specific intentional informed consent toward a model of presumed consent.[27] There are a few indications that this drift is occurring. The first is that proponents of genetic testing often report that individuals are generally in favour of testing and wish to know all results,[37] suggesting that checking with individuals each time is therefore not necessary. A further indication of this drift was the American College of Medical Genetics 2013 proposition that with every genetic test the sequence be examined for disease-causing variants in an additional 56 genes regardless of the initial reason for the test and regardless of the patient's desire to have these elements of their genome examined.[38,39] This directive was modified in 2016 to allow patients to decline this additional review. A final indication that we are moving away from intentional informed consent is the observation that newborn screening has, according to those with this concern,[27] become so routinized so as to be almost mandatory at present. It is not actually mandatory — parents or guardians are still able to opt out. However, the ways in which this screening occurs rarely includes an overt informed consent process.[27] It may be that traditional models of informed consent are not generally feasible or helpful within the context of genomics; and, if this is the case, then a move to a new model of consent should occur thoughtfully and with intention. Those concerned with a drift away from informed consent worry that the drift is due to an exuberance about the technology rather than with due consideration.

Compared with other genetic tests, the consent process for GWS is likely to take more time because of the complexity of the results (specifically VUS and incidental findings). The duty to respect autonomy nevertheless requires that a careful and robust informed consent process be in place for GWS. If GWS is funded, it will be important that implementation allows for careful, and possible lengthy, consent processes to take place, led by skilled and knowledgeable professionals.

Respect for Personhood

A second element of our principle of respect for autonomy and personhood encompasses our duties to recognize others as whole persons to whom we owe dignified consideration regardless of their challenges or abilities. This includes respect for the patients who live with anomalies or delays, as well as respect for the families and communities that surround these patients. Fundamentally, this obligation requires that patients continue to be seen as whole unique people and that they are not reduced to their genetic characteristics through testing.[29] This principle can further be lived up to by using careful and non-discriminatory

language in conversations with and about patients. In interactions with individuals who have anomalies or delays, the focus should be on treating the individual as a person rather than a genetic condition.[17] When interacting with patients and families (especially surrogate decision-makers), respect for persons requires that health care professionals operate with a respect for the basic intelligence of these others regardless of their knowledge, especially given the complexity of genomics.[17]

More broadly, respect for personhood requires that those who are using GWS are aware of the potential for harm that medicalization of people through GWS may bring. The term medicalization refers to the defining of a problem in medical terms.[40] Within the context of GWS, sequencing may turn a phenotype that has been perceived as a social or behaviour problem and that has been addressed by social and behaviour interventions into a medical problem. The risk with defining something medically is that there is a concurrent shift toward solutions or interventions that are generally medical, perhaps moving away from effective and beneficial social interventions (e.g., behaviour support, adaptive environments, etc.).

Respect for Cultural Diversity

Part of respecting individuals as whole persons involves recognizing their diversity and uniqueness. As outlined previously, the principles of respect for autonomy and the associated importance of informed consent is premised on the fact that individuals do not all value the same things. Sometimes these differences align with underlying cultural values and experiences, and sometimes they do not. It is important that professionals, particularly those working in pluralistic societies like Canada, are aware of the influence that cultural backgrounds may bring for their patients.[17]

For instance, within Asian bioethics traditions, family structures for some may have greater prominence in the way that patients engage with health care providers. Further, there may be a greater emphasis on relationship among family rather than considering decisions in terms of individual “rights.”[17] Communication may be more implicit and there may be the potential for greater feelings of shame if a hereditary disorder is uncovered within the family, which may have an impact on whether and how information is shared.[17]

Whatever the cultural background of patients and families seeking genetic services, it is important that the health care providers involved in delivering these services be aware of the potential role that patient or familial beliefs about culture, religion, health, social values, and family structure may play in the therapeutic relationship.[17,41] It is similarly critical that health care providers are mindful not to make assumptions or stereotype individuals based on their backgrounds. A general rule of providing accurate facts as clearly as possible while avoiding imposing personal views is most appropriate for health care providers.[41] Patients with particular religious views may also be challenged by the results of genetic screening. One author has noted that the presence of a genetic variant may raise difficult questions about notions of divine justice, personal guilt, and personal abnormality.[42]

GWS technologies are novel and complex, and can have substantial impacts for the patients and families who engage with them. They are rapidly evolving, prone to misunderstandings, and may challenge individual notions of disease and personhood. Aligning practice with the duty to respect individual autonomy and personhood is crucially important to ensuring the integrity of GWS.

Duty to Protect Confidentiality

Related to duties to respect autonomy, the duty to protect patient confidentiality stresses the importance of individuals having control (either directly, or through the decisions of their surrogate decision-maker) of how their personal information (including health information) is shared and used. This principle is especially relevant to genomics because the information that is generated through genetic testing can be uniquely revealing about the individual whose DNA is tested and to those related to that individual, and because whole genomes cannot meaningfully be anonymized.[7,29] Health care providers and others managing genetic information have a duty to protect the privacy of these individuals and families.[7,17] On a broader scale, those who build and maintain databases of genetic information have a duty of stewardship over that database to ensure its security and integrity. This is crucial to securing the public trust, which is necessary for continuing to build and benefit from such databases.

The primary ethical concern for GWS regarding privacy and confidentiality deals with how individual genetic information should be managed, including questions about who else might have access to the data. This includes access by family members, other health care providers, and institutions.[16] Generally within health care contexts there is a presumption that a patient's health information will remain confidential;[43-45] however, there are circumstances when that data could or should be shared (for example, in instances when others may benefit from the information sharing or at least not be harmed by it). These would be exceptional circumstances that must meet specific criteria.

Given that individual genetic information could have implications for related family members, one of the more pressing ethical questions regarding GWS and confidentiality has to do with sharing patient information with family members. Ideally, conversation about disclosing genetic information to family members would begin in the informed consent process (or pretest counselling) prior to sequencing.[43,44] If information that may be relevant to the family is discovered, prior to disclosing any information it should be determined whether particular family members would like to know information about any genetic risk pertaining to them.[43,44] A decision by a family member not to be told should be respected. If at least a subset of the family wants to know about their genetic risk, then patients should be informed about risks related to the family.[45] Often, this is enough to spur patients to inform these family members directly. If health care professionals feel there is genetic information that should be disclosed to family directly, then they should proceed with disclosure first by seeking the patient's consent.[43,44] Generally, a patient's decision about disclosure to others should be respected [43,44] provided this does not put family members at risk of serious harm.

If sharing information with relevant family members could protect them from harm, then health care providers may find themselves in a true ethical dilemma, where duties to preserve patient confidentiality conflict with duties to protect others from harm. The duty to protect patient confidentiality, however, is not absolute.[7,29,45] There are circumstances where health care professionals are ethically and legally permitted (and sometimes obliged) to break confidentiality, most often in cases where others may be at risk if confidentiality is preserved. If a patient has indicated that they will not share information about genetic risk to family members and has not consented to this disclosure, and the information could help the family avoid serious risks of harm, then the health care provider would be justified in disclosing this information directly to family members.[43-45] When disclosing genetic risk to the family without the patient's consent, health care providers should disclose only the information necessary to enable the family member to avoid the risk.[16]

A second frequently mentioned concern regarding the protection of genetic information is whether non-health institutions such as insurers and employers may be able to get access to the genetic information of current or potential clients or employees. Regarding harms to patients and families as already discussed in the previous section, the *Genetic Non-Discrimination Act* passed in 2017 prevents insurers and employers, among others, from seeking genetic information about clients or employees. In other words, health organizations are not permitted, nor can they be compelled, to share the genetic information they have gathered through research or clinical care.

A third core ethical concern relating to GWS arises with questions about how to build and manage databases containing genetic information. These databases are important for understanding the significance of genetic variants, especially in the case of rare diseases. Most databases collect information anonymously; however, it may still be possible to identify particular patients if the database contains detailed information about sequences, variants, and phenotype.[7] A high level of detail in genetic databases is desirable, as this optimizes their utility: collecting less patient information makes them less valuable. Anecdotal and qualitative data about patients' perspectives on contributing their information to databases indicates that patients (or their surrogates) generally want to share the patient's genetic information [7,28] (Dr. Kym Boycott: personal communication, 2019 Apr 18), as they find meaning in the potential to help others experiencing similar challenges.

Considerations of privacy and confidentiality are not unique to GWS and have generally been well-managed by guidelines and practices within the field of genetics. GWS is, however, unique in the volume of genetic information it can generate and the potential identifiability of the information, and so careful policies and process must be in place to ensure that an appropriate approach to confidentiality continues.

Duty to Promote Fairness and Justice

Principles of promoting fairness and justice can be described in various ways but, in general, outline duties to ensure that public goods are distributed equitably and according to need.[17] In other words, justice and fairness require that benefits and burdens are distributed fairly across society,[11] and that no one social group or community bear disproportionate burdens. As such, this principle is fundamentally about equity and about the extent to which individuals are able to have equal opportunities to benefit from health services, including new technologies.

GWS has the potential to improve health outcomes for those who are able to be tested. It therefore has the potential to "both expand and reduce" disparity among people, depending on who is able to access and benefit from the technology.[46] GWS poses three challenges to considerations of fairness and justice. The first has to do with access to qualified health care providers, tests, and follow-up; the second has to with representation in the reference genomes and the extent to which individuals from various ethnic backgrounds can benefit from genetic technologies; and the third has to do with responsible stewardship of health care resources and duties to allocate resources fairly.

Given the relatively new and specialized nature of GWS, it is unlikely to be equally and widely accessible within the province of Ontario. How GWS is to be implemented if publicly funded would have implications for access for patients. If primary care physicians are able to refer for testing, then patients may have better access to the technology, as primary physicians may be more accessible than specialized genetics services. As already discussed, this comes with risks that the involved physician may not have the same training and expertise as medical geneticists to ensure appropriateness of the test, to guide the

patient through a robust informed consent process, and to protect the patient from some harms. If GWS is implemented in such a way that decisions to pursue GWS occur after referral to genetic services, of which there are comparatively fewer, then access may be quite limited, especially to those outside of metropolitan areas. Genetic counsellors are currently unregulated in Canada, so are not governed by provincial or territorial legislation to ensure standards of care.[47] Stakeholders have noted that the recognition of genetic counsellors as health professionals in every province may help to increase and facilitate access to genetic services.

If a patient is referred to further testing following GWS, they must contend with the fact that, as with many highly technical and specialized health services, those with specialized knowledge and skills tend to be located in larger cities. There are outreach genetic services available in Ontario that offer greater access to those living in rural and remote communities, although even with these outreach clinics, some patients must travel for hours to obtain services (Dr. Kym Boycott: personal communication, 2019 Apr 18). If patients are tested and receive an actionable diagnosis, then there is the further challenge of establishing reasonable access to specialized intervention, monitoring, and other follow-up.[16,17]

To live up to the principles of justice and fairness, health care decision-makers must consider how access to GWS will be organized and distributed, paying particular attention to communities that are likely to either have higher needs or are more likely to have their interests overlooked, such as rural and remote or indigenous communities.[48] The most just arrangement would see programs that are available based on need rather than the ability to pay,[29,46] and address those with the heaviest genetic or phenotypic burdens.[17] Without intentional and concerted efforts to be maximally just, genetic programs risk contributing to health inequities.[48] Of course, differing levels of access to health care services is not unique to GWS; as with other services, it would be undesirable if not impossible to ensure that every resident of Ontario had the same access to GWS, and in fact this is not what principles of justice and fairness require. Rather, such principles require that decision-makers be mindful and work toward building a system that promotes health equity rather than prevents it.

A second consideration of justice and fairness regarding GWS arises in the methods for identifying and understanding the significance of gene variants within patient's DNA sequences. Diagnostic sequencing focuses on candidate variants that are either absent or rare in control reference cohorts, each of which is considered to be a potential explanation for a relevant phenotype.[49] Disease-causing alleles can be distributed along ethnic lines.[30] If a particular ethnicity or ancestry is not well-represented in the reference cohort, then patients from that ethnicity will receive results with many more variants, which makes it more difficult to determine the ultimate cause of their presentation.[49] Available reference genomes tend to disproportionately represent European ancestry.[16] Researchers in the Ontario context have confirmed anecdotally that patients from non-European (specifically those from South Asian and Middle Eastern) backgrounds tend to receive more variants in their results than those from European backgrounds given the lack of appropriate population control data sets (Dr. Kym Boycott: personal communication, 2019 Apr 18). Considerations of justice and fairness require that genomic data are representative of all relevant backgrounds of the population being served. Failing to do so could further contribute to health care inequities.[49]

A third consideration of justice and fairness regarding GWS arises with duties to ensure the stewardship of public resources. This duty requires that scarce health resources are used in a way that maximizes the public good and distributes the benefits and burdens of the resource appropriately. This consideration is especially pressing as health systems continue

to face considerable challenges with containing costs and where advancing technologies are one of the key driving forces behind increasing costs.[46] To live up to duties to steward resources, GWS must first be shown to be of greater value than existing interventions in practice. Some authors have proposed that GWS is of greater economic value because if it yields a diagnosis it could avoid or shorten a patient's diagnostic odyssey, as already discussed. Again, if it yields a diagnosis, it may also lead to the cessation of ineffective treatments. In both cases, the use of GWS could result in a decrease in overall spending on health care for that patient.[46] On the other hand, if GWS is only made available after other tests have failed to produce a diagnosis, as is currently the practice, then it may present an additional cost to the system, rather than cost savings. These costs could grow further if GWS produced an actionable result that included additional treatment and monitoring. While this may be beneficial to the patient, it could still be more costly than if GWS had not been performed.[46]

As has been noted with other therapies (e.g., chromosomal microarray), there is a concern that, with public funding, GWS will become more widely available and thus more widely used with patients for whom it is not indicated. To avoid this outcome, health care providers will have to be appropriately trained and the necessary procedures will have to be put in place to curb inappropriate use.[17] Use of GWS for patients for whom it is not indicated could not only lead to harms for that patient but also constitutes a waste of health care resources.[46]

GWS is not inherently unjust, nor does there appear to be any barriers that would necessarily prevent it from being implemented fairly; however, this discussion has shown that it does have some potential to be used unjustly if it is not implemented in appropriate ways. To best ensure that GWS at least does not perpetuate injustice, it will be important to review how clinical services are organized and delivered, and consider enabling access to GWS according to where the greatest inequities exist in the system.[48] In addition, further efforts should be made to collect and understand data on non-European genetic variation to ensure the production of more reliable results for non-European patients.[48] Finally, training, processes, and criteria need to be established to ensure that GWS is used with the appropriate expertise for the appropriate patients.

Duty to Acknowledge and Protect Vulnerable Persons

In cases where a technology is most likely going to be used with patients who are vulnerable, it is worth being explicit about the duties of decision-makers, health care providers, and others involved in the organization and delivery of health care of the impact of their decisions on especially vulnerable patients. Vulnerable patients can be defined as individuals or groups of individuals who are less able to advocate for themselves or whose interests could be easily or would be likely to be overlooked. This could include children, those with moderate-to-severe cognitive impairments, immigrants and refugees, and others from typically marginalized communities.

The population under consideration for this HTA is individuals with unexplained disabilities and multiple congenital anomalies. Members of this group may be infants or children and they may also have cognitive impairments, both of which make them more vulnerable to the actions of others. The duty to acknowledge and protect vulnerable persons requires that this vulnerability be noted and that special consideration is given to ensuring that the needs and interests of these persons are considered.[17] At a systems level, this requires that decision-makers consider the impacts of their decisions on vulnerable groups. In the clinical or research context, health care professionals must be mindful of the effects of decisions on vulnerable patients and must be willing to advocate for such patients, when necessary.[17]

GWS raises a number of specific issues relating to vulnerability. There are questions about the nature of testing and disclosure of results for patients who are minors or have cognitive impairments. For example, there is debate about whether children (or their surrogates) should be informed of any incidental findings of variants relating to adult-onset disease.[28] For patients with moderate-to-severe cognitive impairments, there is debate about whether, following genetic findings that suggest monitoring, they should be subject to invasive monitoring procedures (e.g., colonoscopy, frequent blood tests) if they are unable to understand the purpose of such tests. Those patients whose genetic heritage is not well-represented in reference databases may also be understood to be vulnerable, especially if these individuals are also members of marginalized groups (e.g., immigrants or refugees), as GWS is more likely to yield false-positives and high numbers of VUS, which could lead to excessive follow-up. Stakeholders have pointed out that there are multiple efforts underway to increase the number of reference sequences for less represented populations including the 100,000 Genomes Project (UK), the Personal Genome Project Canada, and the Silent Genomes Project (Canadian Indigenous peoples), for example. Of particular note to this HTA is that the initial rollout for GWS is being proposed for a population with multiple vulnerabilities (i.e., patients, including minors, with unexplained developmental disabilities and multiple congenital anomalies). GWS exposes patients to many familiar ethical concerns, as well as a substantial and new level of clinical uncertainty that could be a source of harm through burdensome follow-up and unnecessary or inappropriate interventions. GWS could be positioned as a response to this vulnerability in the way that it may meet the needs of this population in a way that other technologies have not been able to, but it could also unintentionally exploit these vulnerabilities.

Attention to the vulnerability of individuals or groups does not supplant other relevant ethical considerations (e.g., respect of autonomy); rather, it requires that special attention is paid to determine whether the individual or group is owed further support to ensure that their interests and needs are equitably met.

Key Issues

Incidental Findings

GWS may reveal genetic information, often a gene variant, that is unrelated to the original purpose for the test but has the potential to be important for health or reproductive outcomes.[24,35,50] These are described as incidental findings. Incidental findings can also include information about biological connectedness, including (mis)paternity, adoption, and unexpected consanguinity. Incidental findings are distinct from secondary findings; the former are findings that are discovered by accident, whereas the latter are findings that arise from the intentional analysis of specific genes.[38] This discussion focuses on incidental findings and how to ethically manage these in the context of research and clinical genome sequencing.

The discovery of incidental findings through testing is not unique to GWS. They are a factor with other genetic tests and have been a subject of discussion in the literature for some time. That said, GWS can produce a much higher volume of incidental findings than more targeted tests. A large volume of incidental findings can take much more time and expertise to sort out,[30] raising questions about appropriate expertise and allocation of resources (in this case, professional time and focus) and may also complicate informed consent processes, as the larger volume of information will require more careful work to help patients understand and make decisions. Given the complexity of GWS, especially in light of the large number of incidental findings it is likely to yield, traditional models of informed consent

are likely to be insufficient.[30,51] Appelbaum et al. [52] have proposed four models of informed consent, three of which are intended to organize the consent process to enable patients (or their surrogates) to understand the information necessary to make decisions and to make smaller decisions over time rather than requiring them to make several complex decisions all at once. Consideration of novel modes of informed consent could lead to more robust processes that are truly respectful of patient autonomy and avoid any distress caused by unmet expectations.

Genetic findings, including incidental findings, can be identified according to the following categories: pathogenic, likely pathogenic, VUS, likely benign, and benign.[32,53] VUS (the third category), which is neither clearly associated with disease nor is likely to be benign, tends to cause the most misunderstandings and frustrations for patients and their families.[32] The uncertain nature of VUS cannot be resolved through additional testing,[54] thus adding complexity to conversations about whether and how to inform patients when such variants arise as incidental findings.

There is substantial discussion in the literature about whether — and if so, how — researchers and clinicians should manage disclosure of incidental findings to patients. There may be a number of benefits to disclosing incidental findings of a certain type to patients or their surrogates. If the findings identify genetic variants that are actionable — that is, there is some action (therapeutic or otherwise) that the patient can take to address the presence of the variant — then disclosure could prevent harms or improve health outcomes.[16] Disclosing incidental findings may also assist patients or related others to make reproductive decisions. Finally, given that knowledge of certain kinds of incidental findings may enable them to make good decisions, patients and their families may find that learning of incidental findings to be clarifying and empowering.[24] Given these benefits, one could argue that disclosing incidental findings, or at least an actionable type of incidental finding, is consistent with duties to create benefit to patients and relatives.

The disclosure of incidental findings also comes with some risks. Knowledge of incidental findings could cause emotional distress and anxiety for patients and families,[9,17] especially if they reveal information about potential disease or information that could disrupt the family structure (e.g., misattributed paternity). The findings may be inaccurate or of unclear significance [24,28] and could lead to risky or unnecessary follow-up testing.[31,50] If they do lead to another diagnosis, this could increase stigmatization for the patient.[24] Finally, similar to the arguments for the “right not to know,” as previously discussed, some have proposed that pediatric patients have a “right to an open future,” which means they have a right to not be burdened with the knowledge of a predisposition to an adult-onset disease.[9] Disclosing findings about adult-onset disease would constitute a violation of this right. There is some potential, then, that disclosing incidental findings without care could cause net harm to patients and their families and so would fail to live up to duties to prevent harms.

Many have suggested that the best way to manage incidental findings is through a robust consent process. This is likely a good strategy; however, it can be complicated to seek consent for a procedure when it is unclear what will be found and what the potential outcomes may be.[28,54] Further, it may be disingenuous to suggest that patients or surrogates have an unfettered choice in the matter, as some have argued that it be mandatory to disclose certain incidental findings, at least in the case of findings relevant to children. If an incidental finding indicates a treatable childhood disease, then the argument is that parents and surrogates must be informed and ought to act to promote the well-being of the child.[17]

There are several proposed strategies for managing incidental findings. These run on a spectrum from sharing all genetic data in an uncurated fashion, to sharing all findings, to

sharing only variants of known significance, to sharing only actionable variants, to sharing no incidental findings at all.[50] If clinicians or researchers plan not to share any incidental findings with the patient, for whatever reason (e.g., patient request), but become aware of some potentially serious or actionable findings, they may be put in an ethically challenging position and could experience some distress if they are not permitted to reveal this information.[55] It has been proposed that, to avoid this circumstance, laboratories should mask results from clinicians where such results will not be shared with patients.

There has been extensive consideration of whether there should be a limit to the type of incidental findings that should be shared. Some commentators suggest that patients should receive whatever they consent to receive.[28] Some propose that only incidental findings that provide a means of improving clinical outcomes be disclosed.[33] Some suggest that incidental findings only be disclosed if particular criteria are met (e.g., they pose substantial risk, are actionable, have been discussed in consent processes).[24] Others suggest that various packages or tiers of information be made available to patients, where the default package would include life-saving data and data of immediate clinical utility.[55,56] As already discussed, many authors advocate for the mandatory disclosure of incidental findings where they include variants that predispose a child or other family members to serious conditions where treatment exists.[30,31] Otherwise, parents could opt out from receiving information about incidental findings.

A few authors have noted that following up on patients' consent to disclose incidental findings can be very time-consuming. For example, one institution estimated it would take five hours of a clinician's time[30] and, in a research context where data has been anonymized, this is not feasible [33] (Dr. Kym Boycott: personal communication, 2019 Apr 18). Efforts to do so therefore can be burdensome and take the focus away from other important research or clinical tasks. It could be argued that requiring the extensive disclosure of incidental findings is a justice issue, as it concentrates resources on fewer patients, thus foreclosing on the possibility to serve a broader group or make further progress toward useful research outcomes.[11]

There are a number of outstanding questions to do with incidental findings related to genome sequencing. The distinction and overlaps between clinical and research contexts are fuzzy and the respective duties of health care providers and researchers involved is not yet clear. There are also unanswered questions about how much access and control patients ought to have over their own data. For example, ought they be able to contact the lab to see all of their incidental findings?[35] There have also been incidences of patients and families taking their genetic data to social media as a means of making contacts with others with similar genetic variants and, in some cases, to diagnose.[57] This shift amounts to a kind of democratization of data, the implications and consequences of which are unknown.

Ultimately, there is no one agreed-upon standard by which incidental findings should be managed. If protocols for managing incidental findings are developed for a particular genetic service, it will be important that they are communicated to and understood by the range of people involved (including data analysts, laboratory providers, clinical geneticists, physicians, and patients and their families).[31] Even with protocols in place, there will likely be times when it should be up to the discretion of health care professionals to determine what to share. In such circumstances, a multidisciplinary approach (including the attending clinician, genetic counsellor, medical geneticists) is likely best to ensure that disclosure proceeds appropriately.[35] Whatever decisions are made, it will be important that patients (or surrogates) are well-prepared for incidental findings through a consent or counselling process, that they have some degree of choice over what findings they receive, that they are

aware of the limits to this choice, and that they are supported in having realistic expectations to avoid distress and disappointment.

Uncertainty

GWS is a new and rapidly evolving technology imbued with substantial uncertainty, which can yield significant variation in results and create ambiguity for patients and providers. Uncertainty is a matter of ethical concern because it can make it difficult to support autonomous decision-making and can yield distress or harms for individuals who are not sufficiently prepared to cope with uncertainty. In short, uncertainty can complicate one's capacity to live up to one's ethical obligations.

General features of genetics contribute to the uncertainty of GWS. Fundamentally, there is uncertainty about the extent to which genetics determine a patient's phenotype and how much other factors (e.g., environmental) play a role.[45] Further, there can be a variation in genomes from person to person, with individuals having their own unique variants.[9] Uncertainty can also arise from errors in genetic analysis; even a very low error rate (one false single-nucleotide variation per 500 kbp [or kilobase pair]) can produces 12,000 errors per genome, effectively creating large numbers of false-positives that may be difficult to interpret.[30]

Another source of uncertainty for GWS arises with its absence of clinical validation to a specific condition. Typically, diagnostic testing is brought into clinical practice only after its characteristics and clinical significance relative to a specific condition have been validated. The implementation of GWS in its current form represents a divergence from the usual approach to new tests because it intentionally involves testing for unknown conditions. Without validation for particular conditions, there is no reassurance that the test will yield any result — which can lead to frustration and distress for patients.

Finally, uncertainty can arise with the laboratory processes used to manage VUS. There has historically been an absence of formal guidelines on data processing and interpretation of variants,[15,31] although there has more recently been a move toward standardization of approaches. Importantly, variant knowledge is rapidly evolving; new variants are being identified and the interpretation of existing variants is changing.[29] Different laboratories that conduct testing adapt to these changes differently on top of their own variations in practices, which can sometimes lead to different laboratories producing different results for the same sample. [16] (Dr. Kym Boycott: personal communication, 2019 Apr 18). Among practitioners, there may similarly be variation in practice with interpretation and managing test results, and in individual assessments of harms and benefits within the context of clinical decision-making.[32]

Some of these sources of uncertainty are inherent to the current state of gene science and so are difficult to change. Others, namely current laboratory and clinical practices, could become more uniform with close quality control,[17] along with a commitment from laboratory staff, researchers, and clinicians to implement and follow clear guidelines and processes. Even with improved consistency of practice, uncertainty will likely remain a factor in GWS, so will need to managed carefully. Without minimizing and acknowledging uncertainty, the informed consent process may be compromised and there is a risk that patients and families will experience distress and other forms of harm by having unrealistic expectations or by starting burdensome medical interventions (therapies, monitoring, research) based on ambiguous results. An honest and humble approach to GWS is warranted.

Professional Roles

The delivery of GWS depends on several levels of expertise. The process and outcome of any single test could be influenced by multiple players — the referring physician, affiliated nurses, the genetic counsellor, the medical specialist, researchers, laboratory technologists, and other analysts. The nature of each of these roles, their required skills and knowledge, and their potential impact on patients will be determined by how access to GWS will be organized — with the primary care physician as gatekeeper or with providers within genetic services determining whether GWS will be offered. GWS may also include elements of research (e.g., collecting genetic information for databases). Those within these roles thus need to be aware of the distinct demands of clinical care versus research and be mindful of the purpose and intentions of their actions as they work with patients and their families. Whatever the case, an ethically optimal implementation and use of a technology depends heavily on the knowledge, skills, and judgments of individuals in each of these roles, and the accessibility of each of these roles to patients and families in need.

Access to appropriate services and expertise is crucial for the beneficial use of GWS. In particular, specialized genetics services and trained genetic counsellors are important for assisting people in having access to relevant knowledge and services, and to support complex decision-making for patients and families who are considering or who have undergone GWS; and to help patients and families cope and understand the results of testing.[17,32,58] This is especially the case if there are large numbers of, or at least significant kinds of, incidental findings to be reviewed and discussed, which is especially possible with GWS compared with other types of genetic testing.

As discussed in the section on justice and fairness, there are concerns that some patients and families will have insufficient access to specialized genetics services, even with existing outreach programs in Ontario, and thus may have no access to GWS; or, that they will be able to proceed with GWS initially but will not have access to the necessary supports to understand the results or participate in meaningful follow-up. This would constitute a failure to live up to duties of justice and fairness, as well as duties to create benefit and minimize harms for patients and families. Given these ethical stakes, it is important that careful attention is paid to determining the appropriate roles for health care providers who could be involved in the delivery of GWS should it be funded.

If GWS is funded, it can be expected that its use will eventually expand beyond those who currently provide the technology to those who are less familiar with it.[36] Education and training will be necessary to ensure that the potential benefits of GWS are translated into clinical care and any potential harms are minimized.[29,30] This education must reach the general practitioners who may be involved in an initial referral for GWS, as well as in the necessary interpretation of results and ongoing follow-up.[16,36] Stakeholders have noted that those with genetic expertise, especially genetic counsellors and medical geneticists, should be involved in the development and delivery of this education. Stakeholders have also noted that the recognition of genetic counsellors as health professionals in every province may help to increase and facilitate access to genetic services. Given the rapid pace at which genome sciences is advancing, it may also be helpful to develop an electronic system that can keep pace with the scientific advances and provide current and evidence-based information to clinicians at the point of care.[46,59]

Ethically sound practice depends on the professionals involved having the required skills, knowledge, and commitments. Implementation of GWS without due attention to this

dimension of the technology could result in harms and inequities, and thus a failure to deliver on key ethical obligations.

Other Issues

The following issues are not of central concern to this HTA but may provide helpful context to deliberations about the public funding of GWS.

Retesting and Duty to Recontact

Knowledge in many aspects of genetic disease continues to evolve rapidly and new information may become available that would be relevant to individuals who have been tested in the past.[7,30] Some authors have argued that there is an ethical duty for researchers or clinicians to remain up-to-date on new developments that may be relevant to previously tested patients and their families, and to recontact individuals who (either directly, via their surrogate decision-makers) have indicated that they wish to be contacted if these new developments may be relevant to their health.[17,31] There is some question about the feasibility of recontacting previous patients and family members. To effectively cross-reference previous patients with developing knowledge, in addition to working with new patients and families, would take substantial resources. Further, some settings do not have the record-keeping infrastructure in place to retrieve files and up-to-date contact information for previously tested individuals.[7] Many clinics have, to an extent, resolved this issue by asking patients to get in touch with genetic services every few years, or if there is a change in family or health status that may be relevant.[7] It could be argued that devoting time to keeping track of new developments, monitoring previous patients' tests, and spending time following up with patients would take important time and resources away from care for new patients who are testing-naive, and so is not an appropriate allocation of energy. Conversely, if this is an important part of genetic services, the work of monitoring and following up should occur within a clinical context rather than a research one, as the former has more infrastructure in place to do so more easily (Dr. Kym Boycott: personal communication, 2019 Apr 18). At this time in Ontario, reanalysis of existing, clinical GWS data is not readily available given that this data resides in diagnostic laboratories outside of Canada (Dr. Kym Boycott: personal communication, 2019 Apr 18).

The Distinction Between Clinical and Research Contexts

As expected, GWS has been developed and refined through research activities so that the early experiences for patients, providers, and researchers were informed by research goals and paradigms. Research and clinical care can be distinguished by their respective general intentions. Research is pursued to create new knowledge that will help improve the well-being of individuals and populations in the future. In the context of health care applications, research plays an important ethical role in identifying technologies that will be of overall benefit to people, while identifying (and thereby preventing the implementation of) technologies that do not offer a balance of benefits over harms. Through these activities, attention is paid to the well-being of research participants; however, the primary goals of research are not to advance their well-being. Clinical activities occur with intentions (and duties) to promote the well-being of the patient receiving care in the present. Although the primary goals of research are not to directly benefit participants, requirements of research ethics that guide most research require that there is due care to ensure that research participants are not disproportionately harmed through their participation in research.

This distinction between clinical care and research is important; however, the nature of and trajectory of GWS has blurred the boundaries between the two. There remains a distinction between experimental clinical practice relating to GWS (research) and the clinical application of the technologies, although within this clinical application there are elements of research. There is the interest and perhaps need of clinicians to gather genetic data to improve the comprehensiveness and utility of genetic databases. There is also the somewhat experimental nature of discovering and understanding VUS that arises in the clinical application of GWS. As a result of this blurring, many policies, guidelines, and proposals in the literature regarding the protection of patients were written for the research context but could, with some care, be translated into policies for clinical applications of GWS.[52]

The primary question posed by this HTA is whether GWS (or one or the other of WGS or WES) should be funded and implemented more fully into clinical use. The results from this research (discussed in the clinical effectiveness review),[13] as well as the research ethics demonstrated to be of importance during this research, will assist in answering this question.

Summary of Results

What Ethical Considerations Arise With Genome-Wide Sequencing?

GWS is subject to many of the same ethical concerns as other genetic tests including considerations of respecting individual autonomy through consent processes, balancing harms and benefits with attention to stigmatization, protecting confidentiality while considering how to protect individuals related to the individual, and how to manage incidental findings. GWS generates some novel ethical concerns, however, due to a high volume of incidental findings and the substantial uncertainty inherent to the technology and the results. Both of these factors can make it difficult to adequately support patients and families through GWS, thus raising the risk of creating harms for the patients the technology intends to help.

Should Genome-Wide Sequencing Be Funded?

GWS has been shown to have the potential to offer a balance of benefits over harms to a subset of individuals with unexplained developmental disabilities and multiple congenital abnormalities, and to their families. It may also reduce the overall costs of genetic testing and so appears to live up to the duties of conferring benefit at a population level and steward scarce resources. Realizing these benefits and reduced costs will depend on how GWS is organized and delivered, and careful attention to this process will be critical to ensuring that funding this technology remains an ethically supportable option.

How Should Genome-Wide Sequencing Be Organized and Delivered?

The promise of benefits from GWS is continuously shifting, which contributes to substantial uncertainty with its use. If GWS is funded, attention will need to be focused on the organization and delivery of services to ensure they live up to the core ethical duties of maximizing benefits over harms, both for individuals and the population; preserving confidentiality; responding to vulnerability; and promoting fairness and justice, particularly to do with access to services. Duties to distribute benefits and burdens fairly require that we are attentive to the accessibility of testing and diagnostic services. Detailed and skilled counselling and informed consent processes will be important to ensure that patients and

families are prepared and have realistic expectations about GWS. Training will be necessary at all levels of care to ensure that health care providers appropriately refer patients to GWS and can accurately interpret the results.

Three key issues deserve special attention: the management of incidental findings, the effects of uncertainty, and the implication for professional roles.

- Incidental findings are results that are unrelated to the original purpose of the test but may be relevant to patients and/or their genetically related family members. Patients (or in the case of those who lack capacity, their surrogate decision-makers) and their families should be informed about the potential for incidental findings and given choices regarding whether they wish to be informed if any arise. If it is the patient's or family's informed decision not to receive certain types of information, it is ethically appropriate for genetic services not to disclose these findings, with some limitations. It can be ethically justified to require mandatory disclosure of incidental findings to parents or guardians in the case of children if the findings reveal substantial and immediate potential harms that may be mitigated through health interventions.
- The rapid evolution of GWS has generated substantial excitement about its promise. It also creates a certain amount of uncertainty about whether the test would ultimately be beneficial, which that can make it difficult to determine specifically what its promise is and for whom. A humble and honest approach in testing, therefore, is appropriate to ensure that patients and families are prepared and have realistic expectations about what the test may provide medically, socially, and emotionally.
- The funding and widespread implementation of GWS will have ethical implications for the roles and duties of various health professionals. If GWS is made available through established genetic services, then it is likely to benefit from the professionals within those services who are already familiar with many of the genetics-related issues that GWS will bring to light. If GWS is implemented in a way that allows primary care professionals to seek GWS directly for their patients, there is likely to be less existing expertise in determining the appropriate use of GWS, thus challenging the assurance of robust informed consent and management of test results including variants of uncertain significance and incidental findings. If the latter approach is taken, it will be important to ensure that the health care professionals involved with GWS have the appropriate tools and training, and it may be important to identify the subset of patients for whom testing will be most useful to avoid crowding out access with patients for whom the test offers little promise.

Conclusions and Implications for Decision- or Policy-Making

The use of GWS appears to be ethically justified. Funding decisions should take into account how this technology may be implemented and the extent it offers a balance of benefits over harms for patients and their families.

Careful and ongoing consent processes with qualified health care professionals will assist in helping patients and families make informed decisions, develop realistic expectations, and prepare for the potential outcomes of sequencing. Consistent practices for protecting patient confidentiality will be important, as well as clear processes for when it is justified to breech confidentiality. It will be crucial to ensure that residents across Ontario have reasonable access to this specialized service, recognizing that it will not be possible for every resident to have the same access. However services are arranged, they ought to be organized to best meet patient needs rather than in ways that privilege particular groups (e.g., those living in metropolitan areas, those who are skilled at navigating health services).

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