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Article abstract

Introduction: Non-invasive prenatal testing (NIPT) allows for genetic testing of a fetus through the analysis of cell-free DNA from the mother's plasma. NIPT is easy and safe for the fetus, since it only requires a blood draw from the mother and therefore holds no risk of miscarriage. It is considered superior to other prenatal screening tests and can also be performed earlier in the pregnancy. NIPT has the future potential for fetal whole genome sequencing (FWGS) for an expanded range of conditions, such as late onset genetic conditions and carrier status. **Objective:** To review ethical, legal, social, and policy implications of the potential use of non-invasive prenatal testing for FWGS. **Methods:** This study is a critical interpretive literature review exploring and reporting ethical, legal, social, and policy implications of potential future implementation of NIPT for FWGS, which will be referred to as non-invasive prenatal whole genome sequencing (NIPW). Database and reference list searching was conducted between 2010 and 2019 for terms related to "non-invasive prenatal testing" AND "fetal whole genome sequencing" and derivatives. **Results:** Following screening, 32 articles were included. Data were grouped into four thematic categories: 1) ethical implications for the future child concerning autonomy and harms, as well as for prospective parents involving autonomy, informed consent concerns, and harms; 2) legal implications including privacy concerns; 3) social implications including changes in family dynamics, altered societal perceptions and disability concerns, justice and equity in accessing the test, and social pressure to use the test; and 4) policy implications including cost and funding concerns, limiting the scope of testing, as well as counseling, education, and support. **Discussion:** The discussion of results highlights several ethical, legal, social, and policy implications of NIPT use for FWGS. These findings have implications on NIPT implementation for FWGS including how the autonomy of the future child should be balanced with the autonomy of prospective parents, the scope of conditions that should or should not be tested for – and covered or not covered by the healthcare system – and the regulation of FWGS introduction, among others. Further research needs to be performed to address these concerns and hence guide the discussion about the clinical implementation of FWGS through NIPT.

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ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Non-invasive Prenatal Testing for Fetal Whole Genome Sequencing: An Interpretive Critical Review of the Ethical, Legal, Social, and Policy Implications

Hazar Haidar[a], Renata Iskander[b]

Résumé

Introduction: Les tests prénataux non invasifs (TPNI) permettent d'effectuer des tests génétiques sur un fœtus par l'analyse de l'ADN sans cellules provenant du plasma de la mère. Le TPNI est facile et sûr pour le fœtus, puisqu'il ne nécessite qu'une prise de sang de la mère et ne présente donc aucun risque de fausse couche. Il est considéré comme supérieur aux autres tests de dépistage prénatal et peut également être réalisé plus tôt dans la grossesse. Le TPNI a un potentiel futur pour le séquençage du génome entier du fœtus (SGEF) pour une gamme élargie de conditions, telles que les conditions génétiques à déclenchement tardif et le statut de porteur. **Objectif:** Examiner les implications éthiques, juridiques, sociales et politiques de l'utilisation potentielle des tests prénataux non invasifs pour le SGEF. **Méthodes:** Cette étude est une revue critique et interprétative de la littérature explorant et rapportant les implications éthiques, légales, sociales et politiques de la mise en œuvre potentielle du TPNI pour le séquençage du génome entier du fœtus, qui sera appelé séquençage prénatal non invasif (SPNI). Une recherche dans les bases de données et les listes de références a été effectuée entre 2010 et 2019 pour les termes liés à « test prénatal non invasif » ET « séquençage du génome entier fœtal » et dérivés. **Résultats:** Après la sélection, 32 articles ont été inclus. Les données ont été regroupées en quatre catégories thématiques : 1) implications éthiques pour le futur enfant concernant l'autonomie et les préjudices, ainsi que pour les futurs parents concernant l'autonomie, les préoccupations relatives au consentement éclairé et les préjudices ; 2) implications juridiques, y compris les préoccupations relatives à la vie privée ; 3) implications sociales, y compris les changements dans la dynamique familiale, les perceptions sociétales modifiées et les préoccupations relatives au handicap, la justice et l'équité dans l'accès au test, et la pression sociale pour utiliser le test ; et 4) implications politiques, y compris les préoccupations relatives au coût et au financement, la limitation de la portée du test, ainsi que le conseil, l'éducation et le soutien. **Discussion:** La discussion des résultats met en évidence plusieurs implications éthiques, juridiques, sociales et politiques de l'utilisation du TPNI pour le SGEF. Ces résultats ont des implications sur la mise en œuvre du TPNI pour le SGEF, y compris la manière dont l'autonomie du futur enfant devrait être équilibrée avec l'autonomie des futurs parents, la portée des conditions qui devraient ou non être testées – et couvertes ou non par le système de santé – et la réglementation de l'introduction du SGEF, entre autres. Des recherches supplémentaires doivent être menées pour répondre à ces préoccupations et ainsi orienter le débat sur la mise en œuvre clinique du SGEF par le biais du TPNI.

Mots-clés

dépistage prénatal non invasif, séquençage du génome entier du fœtus, QEJS, futur enfant, futurs parents

Abstract

Introduction: Non-invasive prenatal testing (NIPT) allows for genetic testing of a fetus through the analysis of cell-free DNA from the mother's plasma. NIPT is easy and safe for the fetus, since it only requires a blood draw from the mother and therefore holds no risk of miscarriage. It is considered superior to other prenatal screening tests and can also be performed earlier in the pregnancy. NIPT has the future potential for fetal whole genome sequencing (FWGS) for an expanded range of conditions, such as late onset genetic conditions and carrier status. **Objective:** To review ethical, legal, social, and policy implications of the potential use of non-invasive prenatal testing for FWGS. **Methods:** This study is a critical interpretive literature review exploring and reporting ethical, legal, social, and policy implications of potential future implementation of NIPT for FWGS, which will be referred to as non-invasive prenatal whole genome sequencing (NIPW). Database and reference list searching was conducted between 2010 and 2019 for terms related to "non-invasive prenatal testing" AND "fetal whole genome sequencing" and derivatives. **Results:** Following screening, 32 articles were included. Data were grouped into four thematic categories: 1) ethical implications for the future child concerning autonomy and harms, as well as for prospective parents involving autonomy, informed consent concerns, and harms; 2) legal implications including privacy concerns; 3) social implications including changes in family dynamics, altered societal perceptions and disability concerns, justice and equity in accessing the test, and social pressure to use the test; and 4) policy implications including cost and funding concerns, limiting the scope of testing, as well as counseling, education, and support. **Discussion:** The discussion of results highlights several ethical, legal, social, and policy implications of NIPT use for FWGS. These findings have implications on NIPT implementation for FWGS including how the autonomy of the future child should be balanced with the autonomy of prospective parents, the scope of conditions that should or should not be tested for – and covered or not covered by the healthcare system – and the regulation of FWGS introduction, among others. Further research needs to be performed to address these concerns and hence guide the discussion about the clinical implementation of FWGS through NIPT.

Keywords

non-invasive prenatal screening, fetal whole genome sequencing, ELSI, future child, prospective parents

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INTRODUCTION

Twenty years following the first publication of the human genome sequence, a staggering decrease in the cost of genome sequencing has been shown, from almost USD$100 million to approximately USD$1000 (1). With continued advances in science and technology, the cost of sequencing the human genome will continue to decrease. The landscape of techniques to advance the field of genome sequencing are constantly changing, making genome sequencing more accessible, common, and efficient; and a technology that will be inevitably deployed as part of individual and population-wide genetic testing.

Non-invasive prenatal testing (NIPT) allows for genetic testing of a fetus through the analysis of cell-free DNA from the mother's plasma to screen for fetal abnormalities including chromosomal aneuploidies, such as Down syndrome, sex chromosome anomalies, and microdeletion and microduplication syndromes (2). NIPT entered the market in 2011 and has been rapidly introduced into prenatal practice (3). NIPT is more accurate than the existing prenatal screening tests (e.g., maternal serum screening) and is therefore considered to be superior (4,5). Further, NIPT is easy and safe for the fetus, since it requires a blood sample from the mother (6) and therefore holds no risk of miscarriage compared to other invasive diagnostic procedures, such as amniocentesis and chorionic villus sampling. It can also be performed early in the pregnancy at about the eighth or ninth week of gestation (7).

In the near future, NIPT can potentially be used for fetal whole genome sequencing (FWGS) as shown by proof-of-principle studies (6,8). FWGS determines the complete DNA sequence of the fetus, which is not yet clinically available, but has been developed in the research setting (8,9). Non-invasive prenatal testing using FWGS – also called non-invasive prenatal whole genome sequencing (NIPW) – might offer parents a vast range of complex information related to the fetus such as: variations of unknown significance, non-medical traits (e.g., eye colour, athletic ability), carrier status, susceptibility genes, and late-onset genetic conditions (e.g., Alzheimer's disease) (10,11). The integration of this technology into prenatal care will present key challenges at the ethical, social, legal, and policy levels. For instance, concerns are raised about the psychological burden (i.e., anxiety and stress) that the quantity and complexity of information will pose for prospective parents and the threat to their future children's autonomy by infringing on the right to choose whether or not to know their genetic information.

To our knowledge, a critical interpretive review on the ethical, legal, social, and policy implications (ELSI) for the potential future use of NIPT for FWGS (i.e., NIPW) has not been conducted. Our review is thus timely, given the ongoing clinical development of NIPT for FWGS and the need to identify and address ELSI raised by this technology. Finally, this review offers general suggestions as starting points for policy considerations in this ever-growing field.

METHODS

Study design

A critical interpretive literature review (12) was conducted to identify and analyze ten years of literature concerning the ethical, legal, social, and policy implications of NIPT for FWGS. Critical interpretive literature reviews focus on capturing and analyzing "key ideas" relevant to the research question (13), i.e., by analyzing the literature as a whole, generating theory, not excluding literature based on rigid criteria, and reporting the search strategy (12,13).

Eligibility criteria

For screening literature results, we included: studies that address non-invasive prenatal testing using fetal whole genome sequencing; English or French language articles (regardless of country of origin); studies published between January 1, 2010 and December 31, 2019; peer-reviewed or published work in journals (e.g., systematic reviews, meta-analyses, case reports, theoretical literature, commentaries, as well as empirical research including qualitative, quantitative, and mixed methods research); and grey literature, if available (e.g., national and international policy reports). Excluded were clinical studies (e.g., randomized controlled trials, cohort studies, controlled trials, epidemiological studies, animal and *in vitro* studies), thesis dissertations and conference proceedings or abstracts, and public opinion articles from non-experts.

Information sources

Information sources included the following electronic databases: *Medline*, *psycINFO*, *PubMed*, *PubMed Central*, *Scopus*, and *Web of Science*. Relevant grey literature and other academic papers were also collected through individual searching (e.g., snowballing from list of references, and Google searches).

Search strategy

The following search strategy was used to identify literature in the electronic databases: (NIPT OR non-invasive prenatal testing OR NIPS OR non-invasive prenatal screening) AND (non-invasive prenatal whole genome sequencing OR non-invasive fetal genome sequencing OR NIFGS OR fetal whole genome sequencing OR *WGS OR prenatal whole genome sequencing OR cell-free fetal DNA OR cell-free DNA). Secondary search procedures included: reference list searching, forward citation searching, and searching in journals. The search strategy was evaluated by comparing search results to a subset of relevant literature previously chosen by the author (HH).

Selection process

Covidence software was used to first screen sources by removing duplicates, then by reading titles and abstracts. Two reviewers (HH and RI) independently screened titles and abstracts, as well as full-text documents for studies meeting the eligibility criteria. Both reviewers extracted data independently from the included full-text articles and then compared results to reach a consensus.

Data management, collection, and synthesis

Data results were recorded and maintained on Microsoft Excel and NVivo 12 (QSR International) and references were managed using Zotero. Both reviewers (HH and RI) extracted data from the literature by recording relevant information, including title, author, publication year, country of study, study type or design, sample population, objectives, important quotes, and comments on the ELSI of potential future uses of NIPT with FWGS. The ELSI data were extracted using NVivo 12 by coding quotations and categorizing them under themes based on a codebook developed by the authors. The codebook listed key themes and ideas present in the ELSI literature on the potential future uses of NIPT with FWGS. The codebook was refined and finalized throughout the data extraction process to reflect the different implications and common themes.

RESULTS

Screening results

Following the screening process, which initially identified 3334 articles in the search, a total of 32 articles were included in the synthesis (14) (Figure 1), and these were used for data extraction and coding of relevant themes in NVivo 12. Of the 32 articles, most articles are from 2017 (Figure 2) because of responses to a target article (15). Also, more than half of the included articles had corresponding authors from the United States, with other common countries being the Netherlands, the United Kingdom, and Canada.

Figure 1. PRISMA diagram for source selection

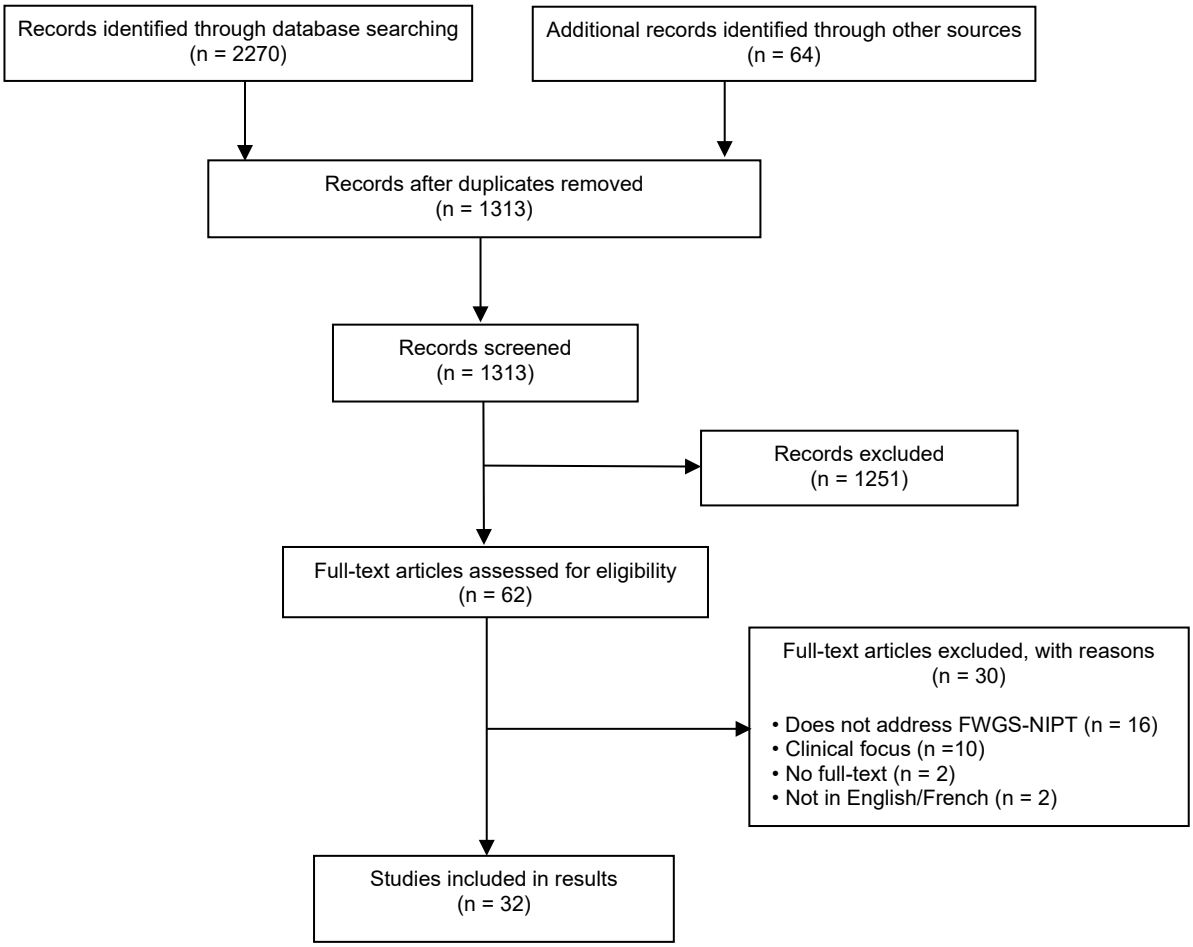
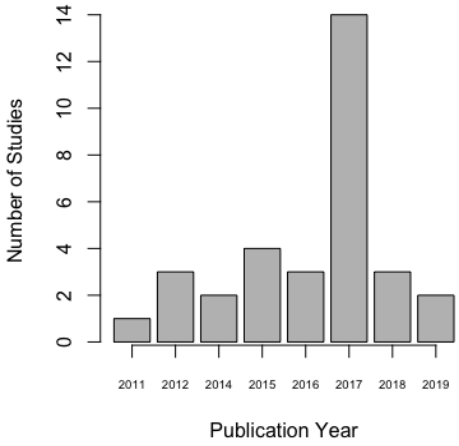


Figure 2. Year of publication for included studies



Data Extraction Results and Critical Analysis

There are various terms used to refer to FWGS through NIPT, including non-invasive prenatal whole genome sequencing (NIPW) and prenatal whole genome sequencing. For the current paper, we will use the acronym "NIPW". The following results show the categorization of themes as ethical, legal, social, and policy implications (ELSI) of implementing NIPW. Reviewers (HH and RI) organized themes independently and then consolidated and finalized through discussion. As shown in Table 1: 1) *Ethical* implications are separated into implications for the future child (1A) and implications for prospective parents (1B); 2) *Legal* implications include privacy concerns related to the future child; 3) *Social* implications explore changes in family dynamics, altered societal perceptions, equity in accessing NIPW, and societal pressure to test; and 4) *Policy* implications examine cost and funding concerns, limiting the scope of NIPW testing, as well as counselling, education, and support. Some subthemes involve overlaps and can be discussed from different perspectives (e.g., privacy concerns are discussed as an ethical implication and a legal implication).

Table 1. Themes and subthemes of ELSI of NIPW

1) Ethical	**(1A) Future child** • Future autonomy • Harms	**(1B) Prospective parents** • Parental autonomy • Harms • Informed consent
2) Legal	• Privacy concerns	
3) Social	• Changes in family dynamics • Altered societal perceptions and disability concerns • Justice and equity in accessing NIPW • Social pressure to use NIPW	
4) Policy	• Cost and funding concerns • Limiting the scope of testing • Counseling, education, and support	

1A) Ethical implications for the future child

The literature recognizes the importance of considering both future children and potential parents in decisions about NIPW, as they are both key stakeholders if the technology is to be implemented. The literature discusses future children's rights to autonomy by invoking their right to know/not to know their genetic information, their right to an open future, and future privacy. Further, it discusses potential harms to the future child such as anxiety and other psychological burdens.

Future autonomy

One of the most noted ethical implications of NIPW relates to the autonomy and right to self-determination of the future child. In the context of NIPW, authors often referred to a diversity of terms to discuss children's future autonomy, including the child's "right to know" (16) or "right not to know" (10,15-22) genetic information about themselves, "right to an open future" (15,16,18-25), and future privacy or other references to privacy (21,23,25,26). Several sources acknowledged that NIPW can raise concerns surrounding autonomous rights of future children (10,16,18-21,27). Authors explored how genetic testing can prevent

the right of future children to choose between knowing and not knowing certain information about themselves at a later age and that there would be more harm than good by not respecting this right to choose (16,19). Several other sources discuss how this technology could threaten the autonomy and interests of future children by removing their ability to decide whether they want to access this information (18,21,27,28).

While some sources expressed these concerns over autonomy, Bayefsky and colleagues found that the negative impact on the child's ability to make decisions upon reaching adulthood was of least concern to obstetricians and gynecologists who were surveyed (17). In the same vein, Rhodes believes that autonomy cannot be violated in this case "because no one can thwart a capacity that does not exist" (22, p.35) since fetuses and young children do not have decisional capacity. Rhodes compares the imposition of NIPW on children to how doctors and parents impose vaccinations and other treatments without consent (22). Further, Deans and others make a similar comparison with school attendance and healthy eating habits that parents might impose on their children, by citing this "soft paternalism" as being justifiable since it holds long-term benefits for the future adult (e.g., securing employment) (23). However, they view testing for adult-onset conditions as a form of unjustified "hard paternalism" because it impedes on the child's private sphere by limiting their (future) choices of choosing not to know such information (23).

The respect for autonomy argument ties closely to the child's "right to an open future" – a phrase coined by American philosopher Joel Feinberg – to indicate that "respect for children as future persons requires safeguarding their future autonomy" (16, p.536). For instance, several articles cite the child's right to an open future as being threatened in the context of NIPW (16,18,20,21,24,25). The Nuffield Council on Bioethics raises the argument about allowing future children to make their own choices in order to access the same opportunities as those who do not know their genetic makeup, which would leave their future open and respect their decisional autonomy (21). They describe this right as being "'in trust' that could be violated in advance by the use of NIPT to identify genetic information about them" (21, p.108). The right to an open future can be threatened by removing life options, such as options concerning education, employment, housing, lifestyle, and other aspects of one's life that may be changed because of knowledge from NIPW (21). However, given that parents inevitably shape and change the course of their children's lives, the right to an open future argument is not universal. Some question whether parents ought to leave their children's futures open. Rhodes denies this argument and does not believe the technology would jeopardize the child's open future because the results would not threaten or impede on the child's abilities (22).

This right not to know is prevalent in the NIPW literature because it relates directly to autonomy and choices future children can make about their future. NIPW can undermine the right not to know genetic information (10,18,28) and some articles cited the right not to know unless the genetic information is medically relevant during childhood (18,20). While the right not to know is advocated for in most of the articles included in our review, Rhodes denies this as a right and instead argues that there is a *prima facie* duty to be informed (22). The author explains that there is no right not to know information that is relevant for decision-making, thus testing the fetus is not violating this nonexistent right (22).

Finally, some authors raised concerns about how NIPW might invade the privacy of future children (21,23,25). According to the literature, learning of genetic information can impede on the informational privacy of the future child by sharing confidential information with parents and/or other parties that can threaten the future child's autonomy (21,23,25). There were no references in the literature we reviewed that explicitly denied the right to privacy of future children; however, the literature shows that protecting informational privacy is in the best interest of the future child. Deans and colleagues argue that not testing a born child to protect their privacy as a future adult should also be applied to not testing a fetus (23). They argue that facts about someone's future invades their private sphere and "knowledge about a person's adult-onset conditions is exclusively the business of the at-risk individual, not her parents" (23, p.7).

Harms to the future child

The ethical principles of beneficence (protecting individual welfare) and non-maleficence (ensuring no harm) are significant considerations in the NIPW literature. Few articles mention beneficence *in utero* and protection of the fetus (29,30) as justification for NIPW use. In that line, Deans and colleagues explain that arguments "against testing a foetus for information for the sake of that being […] would have to rely either on the foetus having rights and interests at the time of being a foetus, or on the claim that the future child or adult has interests that ought to be safeguarded in advance" (23, p.7). Most articles used beneficence of the future child as a guiding principle for NIPW implementation (10,28,30). Informational harms on the child may become apparent upon learning of certain genetic information, such as adult-onset conditions or other trivial information (11,16,18,19,21,23).

As part of balancing the risks and potential benefits of NIPW for future children, the literature explored the psychological effects and burdens that NIPW may have on them (16,19,21,23). For instance, learning of genetic information may result in a child experiencing anxiety or stress, including future development of a certain disorder (23,25). Psychosocial harms may include damage to self-esteem, parental over-protectiveness, discrimination, and stigmatization over knowing certain conditions (16,21,28). While these sources argue that genetic information, especially in relation to adult-onset diseases, can be psychologically damaging for future children, Rhodes opposed this view, stating that there is insufficient evidence to support psychosocial impacts (22). Rhodes argued that it is unavoidable that any decision made – whether or not to test – will affect the future child in some way by having knowledge or ignorance of their genetic information (22). Thus, it seems that while it is conceivable that genetic information can result in negative effects on mental health, further evidence is needed to solidify and justify this claim.

1B) Ethical implications for prospective parents

Some prospective parents may derive great benefit from exercising their parental autonomy and right to know the genetic make-up of their future children in order to decide about pregnancy management. However, others may experience negative consequences such as information overload that might impede their informed consent.

Parental autonomy

The most widely discussed ethical implication for prospective parents regarding NIPW is their autonomous right to test for genetic information and their freedom to choose to continue or terminate the pregnancy. In the literature, various terms are employed to discuss and refer to parental autonomy including: reproductive decision making (10,11,15-18,24,25,29,31,32), informed choice (15,16,18,19,21,24,33), procreative freedom (15), and reproductive choice (10,15,16,18,19,21,25,27-29).

Many sources argue for supporting parental autonomy and informed choice (16,25,27,28,30,33). Chen and Wasserman proposed an unrestricted policy for NIPW under which prospective parents "could obtain information on any genetic variant known to substantially raise the probability of any condition or trait relevant to their reproductive decision making or planning" (15, p.4). They believe that adopting this policy will increase procreative freedoms and inform reproductive decision-making, which respects parental autonomy (15). Rhodes concurs with the policy and states that "just as we should regard people who never want to assume any of the responsibilities of parenthood as free to avoid procreation, we should regard people who choose to avoid the exceptional obligations to a child with special needs as free to reject that parental role and abnegate any related commitments" (22, p.35). However, to further support parental autonomy under this policy, an understanding of parents' perspectives on and preferences for these decisions need to be considered (34). The literature reveals that prospective parents should make informed reproductive decisions and that their autonomy is rooted in parental responsibility (16,19,27,28). Similar to Rhodes (22), Yurkiewicz and colleagues compare autonomous decision-making regarding NIPW to the broader autonomy that society offers to parents such as freedom to raise children according to personal values, free from government interference (28). Exploring parental autonomy, Ravitsky and others argue that NIPW does not lead to enhanced autonomy but instead might hinder it, for example, by burdening prospective parents with a vast amount of information (32).

Parental autonomy is associated with the right to know information about future children because it has implications on reproductive decision-making and therefore, pregnancy management. Based on the literature, this right to know might be stretched from an unlimited right of prospective parents to access any information about the fetus (16,21,28,35) to a more limited right to know of certain information that is "meaningful" or "useful"[1] (15,18,19,25,27,30,31,35) to make an informed decision without specifying the nature of this information (i.e., whether it is medical or not). Richardson and Ormond add that while any piece of information can be valuable to parental reproductive decision-making, it should be recognized that harms could arise from this knowledge in terms of stress and anxiety (35). Deans and colleagues discuss the ethical implications of testing "purely for information", which includes learning information about the fetus either to help parents bond with their future child or to satisfy their curiosity, with no further intended action (e.g., pregnancy termination) (23). In this regard, they conclude that it is unacceptable to test the fetus for adult-onset conditions, carrier-status, and non-serious traits. Dondorp and others believe that neither claims of the right to know and the right not to know information about the future child are founded, because claiming a right not to know for actionable and beneficial information is as contested as claiming a right to know over non-actionable findings and those for late-onset conditions (16).

From a legal viewpoint, and given the current state of genetic testing, a woman who gets NIPT can access all the information this technology produces without healthcare provider interference (36), which would be translated into a vast amount of information once NIPW is clinically available. If no clear guidelines are introduced with NIPW, conflicts will be exacerbated between healthcare professionals and prospective parents over what information parents should have access to, which might lead to diminished trust in physician-patient relationships (10).

Harms for prospective parents

The impact of NIPW on prospective parents and the resulting harms are mainly discussed in terms of psychological harms including stress, anxiety, and confusion (11,15,19,21,23,25,28-30,32,35,37). For example, the right to know certain information about a future child, including variants of unknown significance (i.e., genes with uncertain functions or significance to health) can lead to negative psychological impacts on prospective parents, such as anxiety and stress, leading to concerns over information overload and adequate result management (10,24,38). The complex information included in NIPW can lead to increased stress when compared to information resulting from testing for only selected conditions. Several sources recognize the unnecessary anxiety that could result from learning of information about their future child (10,11,21,23,24,28,29,35), as well as false reassurance and decision stress (19). Not only could NIPW lead to unnecessary anxiety, but also "a loss of enthusiasm for a previously wanted child" (15, p.9) due to unwanted or unexpected genetic test results. While learning of genetic information can lead to distress, decisions about how to act on the information can also foster anxiety and confusion for prospective parents (10,19,37,39).

Nevertheless, another argument in the literature stated that learning of genetic information can lead to preparation for a child with special needs or to reproductive decision-making that can reduce psychosocial distress by avoiding suffering for the future child (25,27). On another note, harms to prospective parents have been discussed in terms of physical risk to the mother. For

[1] "Useful" is not well-defined in the literature and varies by source. Chen and Wasserman acknowledge that different people find different information to be "useful" (15). Richardson and Ormond believe that for some families, any information, even if uncertain, may be useful in making autonomous decisions (35).

instance, there is reason to believe that implementing NIPW could lead to changes in the prevalence of invasive diagnostic procedures, such as amniocentesis. If NIPT became a diagnostic test, it could lead to a decreased need for invasive diagnostic procedures, especially if women are currently being offered invasive tests (11). However, since it is currently only a screening test, the increased use of NIPT can lead to increases in invasive diagnostic procedures, which could lead to harms not only to the fetus (i.e., miscarriage risk), but also physical and psychosocial harms to the mother (19,21,27). In addition, NIPW could have high false-positive rates when initially implemented, which could lead to unnecessary invasive diagnostic procedures (31,32).

Informed consent

In addition to the previously mentioned psychosocial harms that come from learning of genetic information, there is a risk of decisional conflict, which can be understood as anxiety influencing reproductive choices that can lead to future regret (10) or general regrets over reproductive choices and decisions about genetic testing (29). This dilemma is a consequence of a lack of informed decision-making and consent for NIPW. Informed consent may not only be impeded but also may lead to decisional regrets because of information overload from the complex and expansive information resulting from NIPW. For example, while Chen and Wasserman believe that prospective parents will be overwhelmed by the quantity of results of NIPW under an unrestricted policy, they believe that a restricted policy will enhance confusion (15). However, commentators disagree about the unrestricted policy framework because it involves an overly comprehensive consent process that would lead to excessive information that could then impede decision-making (27,29,32,34,40). Another argument is that processing complex genomic data could lead to decision-making that is inconsistent with the preferences of prospective parents (25,29). Unlimited choices may threaten reproductive autonomy instead of supporting it because unlimited choice complicates decision-making and therefore undermines informed consent (10,16,18,19,24).

In addition to causing information overload, the literature shows a focus on ensuring that consent is comprehensive and that parents understand the risks and potential benefits (11,18,24,41). One concern is that parents and healthcare professionals may view NIPW as routine care and will not consider those risks and benefits carefully (36). Changes in norms of parents being expected to act on information because of test implementation may also lead to changes in pregnancy expectations that will complicate informed consent (10). Expanding the test beyond well-known conditions, such as Down syndrome, can lead to difficulties in ensuring parents receive meaningful options for reproductive decision-making and hence hinder their informed consent (19).

2) Legal implications

While the literature is not as yet focused on the legal implications of NIPW, an ethical consideration that could be equally discussed from a legal viewpoint is privacy concerns for the future child.

Privacy concerns

The informational privacy of the future child as an ethical implication has also been explored from a legal perspective, including data storage and management, i.e., how this data should be stored, analyzed, and mined, whether it should be destroyed, who should make decisions surrounding the data, and who has control over it (11,21,26). These issues are also considered to be legal concerns that might affect policies surrounding NIPW because of privacy laws that safeguard health information. Another implication related to privacy is the potential for discrimination in health insurance – based on the genetic information – against individuals who had their fetal genome sequenced, and who may experience difficulties accessing certain goods and services if insurance companies or employers had access to their personal information (21,26).

3) Social implications

Implementation of NIPW could lead to both negative and positive societal outcomes. For instance, a positive outcome could include the improvement of prenatal care as well as pregnancy and delivery management (31). Further, data obtained from testing could lead to advances in biomedical research to help treat conditions with no cure; patients could promote research and join advocacy organizations, which would lead to positive societal outcomes (28). However, there are also negative outcomes that require further discussion to determine the balance of risks to benefits, which we grouped under the following four themes: i) changes in family dynamics, ii) altered societal perceptions and disability concerns, iii) disparities in test use and access, and iv) societal pressure to test.

Changes in family dynamics

When children are born who have been tested for certain conditions, there is a risk that parents will treat these children differently based on their genetic traits. Treating children differently can lead to biases in how parents choose to raise children, can alter relationships between family members, and can ultimately affect the child's life course (10,17,21,28). Knowing this information can lead to parents either having higher expectations of their children and being less accepting of flaws (17,23,29), or having lower expectations of their children and not encouraging their success. For example, parents who learn that their child's predicted IQ is low may become more tolerant of poor academic outcomes, which leads to less parental support and negative effects on the child's success (10).

Chen and Wasserman view these changes positively, believing that parents who know that their children are susceptible to certain conditions will lead to a higher appreciation of the fact that no baby is perfect (15). It could also have a positive effect

for susceptibility genes if parents are aware of them and can influence the incitement of strong genes or suppression of poor genes. For example, if it is known that a child is susceptible to lung cancer, parents can act on this knowledge by educating their child and not smoking around the child to suppress the gene (10). While this may lead to positive outcomes, upon learning of adult-onset conditions, parents may also view their child as vulnerable despite them being healthy as children, which can lead to harmful treatment or stigmatization (23,24). There can also be further changes to expectations of children as well as an understanding of what having a normal or healthy baby means (10,21). While parents may have low expectations upon learning of poor genes, parents may also have expectations for a perfect child and value having control over their child's genes (42). Donley and colleagues also discuss the possibility of the "self-fulfilling prophecy", which is a "worry that the anxiety caused by awareness of one's susceptibility to a condition, as well as parental expectation for the disease to develop, might actually increase the likelihood of the condition manifesting in the child" (10, p.10). Learning of genetic information can lead to changes in family dynamics and how parents choose to raise their children, which includes the possibility that children will be objectified or have their worth determined by their genetics. Viewing children based on their successes or failures because of their genetic traits does not acknowledge them as persons and could lead to them being viewed as commodities (21,23,28).

NIPW may also alter family dynamics by providing prospective parents time to plan for the birth of an affected child by catering to their needs based on knowledge from testing (21,38), which could be viewed as beneficial for the future child (30). There is also discussion around how psychological preparation could lead to parents being more supportive as well as the benefits for the child to psychologically prepare for the development of their own conditions (23). In addition to emotional (19,38) and psychological preparation, "parents may also be better able to put in place social, practical and financial arrangements for care of their child" (23, p.5). Learning of test results can inform choices about plans during pregnancy, such as whether to continue the pregnancy and plan for the birth of the future child with a disability, or to choose termination (21,28). Although there is currently no evidence that preparing for the birth of a child affects their future (40), it is of interest to further elucidate whether preparation (if any) influences the life course and outcomes for children.

Altered societal perceptions and disability concerns

Beyond altering perceptions within family units, widespread use of NIPW could affect societal perceptions and social norms. Similar to how parents may view the ideas of "normal" and "healthy" differently (10,21,27), it may cause society to re-examine how we value persons, what it means to be human (36), and how we view the role of children and parents (42).

Altered societal perceptions of how to define "normal", "healthy", or even our conception of "the good life" (24) can result in discrimination against conditions that fall below newly defined thresholds (21,25,28). It is important to explore whether implementation of NIPW will lead to stigma against individuals who have conditions that are in the scope of NIPW testing. In Chen and Wasserman's unrestricted testing policy proposal, they believe that limiting tests to certain conditions would exacerbate discrimination and convey to those living with said conditions that they are a burden on society, whereas if testing included any and all conditions or traits as they propose, it would not send this discriminatory message and would put all conditions on the same level (15). They believe that the more restrictive the list of conditions, the more stigmatizing the test will be for those living with the conditions on the restricted list (15). Commentators do not wholly agree with this claim and think that it could instead lead to devaluation of individuals with conditions who were not previously included in testing programs, such as those with Alzheimer's disease (39). Shakespeare argues that Chen and Wasserman's proposal for unrestricted testing policy may lead to people being devalued as persons with strengths and weaknesses, and instead viewed as having functional faults (37). Shakespeare also claims that we should be accepting of diversity and support those with disabilities by allowing inclusivity and accessibility, especially when many conditions are not severe and do not discount the worth of individuals (37).

The concerns surrounding endorsement of disability discrimination has also led to the slippery slope concern that more testing will lead to further scrutiny of minor abnormalities (e.g., short stature) or cosmetic and non-medical traits (e.g., intelligence, hair colour) (19). There is also concern that changes in perceptions and expectations of children might lead to parents wanting the freedom to have designer babies by choosing traits based on parental values and preferences (17,21). Beyond this is the concern that NIPW will lead to eugenics, which can be understood as any attempt to improve the genetic traits in a population (21). Several sources (17,32,37,41) discuss the possibility of the increases in discrimination and the push towards testing for and acting on less severe conditions as akin to eugenics. However, Rhodes believes that this slippery slope argument is fallacious because NIPW will lead to more freedom, rather than negative consequences (22).

With an increased uptake of prenatal genetic testing and the expansion of the range of conditions that can be tested, there is a possibility for increases in the rate of pregnancy terminations (10,17,21,28). There is concern that parents might choose to terminate based on variants of unknown significance, or trivial or non-medical characteristics (43). The literature also expresses concern that with increased termination rates, there will be a trivialization of abortion and abortion decisions (18,19,25,27). Trivialization involves the concern that increased termination is because of unimportant or discriminatory reasons, instead of reasons such as avoiding suffering for the future child (27). While some argue that increased termination will exacerbate discriminatory attitudes for persons living with the tested conditions, others believe that terminating a pregnancy because of the possibility for disability is not the same as discriminating against persons living with the same disability (18). Chen and Wasserman argue that because there is limited attachment to the fetus earlier in the pregnancy when NIPW is conducted and that pregnancies are not yet disclosed, it may make termination decisions easier (15). NIPW may also lead to safer and less costly pregnancy termination because the prenatal test can be done earlier in the pregnancy (11). Increases in testing can also lead to termination of *wanted* pregnancies, which can exacerbate previously discussed psychological anxiety and distress

for prospective parents (37). Some sources (21,32) suggest that these increases in termination rates can be seen as encouraging eugenic attitudes, an ensuing result of the slippery slope.

In addition to the consequences of increased termination rates, the social implications of NIPW also include societal imbalance, such as gender imbalances (e.g., resulting from terminating pregnancies based on sex selection) or genetic imbalances and decreases in population diversity as a result of parents selectively terminating based on certain conditions. Furthering prenatal genetic testing can lead to changes in how we value diversity and tolerate differences (24,25,37). Selective terminations can lead to potential harms in society because this threatens biological benefits of genetic diversity, which are known to help with adaptation to changing environments and other survival characteristics (21). However, Berkman and Bayefsky deny that such imbalances will lead to population-level shifts, but that the true effects of selective termination resulting from widespread use of NIPW with regards to decreasing genetic diversity should be explored (29).

Justice and equity concerns in accessing NIPW

Another social implication of implementing NIPW is the disparities in test access and use. NIPW might be expensive, which could indicate that more affluent individuals of higher socioeconomic status would be able to take advantage of it, therefore raising inequalities in access to testing based on income (11,24) or what Chen and Wasserman qualify as “genetic inequality” (15). Such situations might lead to disadvantages for those who cannot afford the test because they will more likely suffer the negative effects of increased invasive testing (11). Tabor and others also believe that it is possible that children with undesirable conditions will be disproportionately born to lower income families who could not afford NIPW, therefore extending societal imbalances and loss of diversity as previously discussed (11).

On another note, the inequity in using the test might be correlated to other factors such as religion, ethnicity, and education (41). For instance, patients with higher education levels may have a better understanding of the test and its results, which might eventually lead to disparities in informed decision-making surrounding testing and reproductive decisions.

Societal pressure to test

Another social implication discussed in the literature that can arise from the future use of NIPW is the societal pressure to undergo prenatal testing. With potential widespread and routine use of NIPW, it is likely that more women will feel pressure to undergo testing to learn about fetal information (10,11,15). There is concern that this will lead to undue commercial pressure to receive test results because of the push towards categorizing testing as necessary for protecting the future child, which incites a strong commercial interest in expanding the market for NIPW (29,34). Commercial push for NIPW and a lack of genetic counsellors might lead physicians to rely on genetic testing companies for counselling, which introduces a conflict of interest due to company-affiliated genetic counsellors providing counselling, which in turn, might increase pressure on parents to accept screening for high amounts of information (29).

In addition to societal and commercial pressures to undergo NIPW, there exists a pressure to act on the test results. Once prospective parents succumb to the pressure of agreeing to testing, they may also experience pressure to act on the results (10,36), therefore threatening parental autonomy (11). Chen and Wasserman express this sentiment when they claim that women who decide to continue their pregnancies have “a moral duty to seek medical intervention for a preventable or treatable fetal condition, if the intervention does not impose too great a burden on her” (15, p.10). This reveals how societal pressure to act can manifest and influence reproductive decision-making for prospective parents who undergo NIPW, including the decision to terminate (11,25). In fact, there is a belief that pressure to terminate reverses social progress towards civil rights and social support for individuals and families with these “undesirable” traits and disabilities (11).

While there is a possibility that parents will experience pressures to use NIPW and act on test results, there are also claims that there is currently no clinical need for the test, and parents currently have no interest in undergoing the test because it does not influence decision-making (38,42). Kraft observed this stating that pregnant women were more interested in choosing a name or finding childcare than they were in talking about the child’s genome (34). However, once NIPW is clinically available, it will be important to understand the impact on demand for testing.

4) Policy implications

Policy implications relate to how policies and guidance surrounding NIPW will be implemented. Relevant policy implications we identified in the literature include: i) cost and funding concerns, ii) limiting the scope of NIPW testing, and iii) counselling and support for prospective parents.

Cost and funding concerns

NIPW will be expensive for years after it is first implemented (21). Policies need to address how funding will be organized to reduce disparities and avoid genetic discrimination of health and life insurance. Costs need to be considered for maintaining support for prospective parents (40), clinical time for patients (24), and education for clinicians (40). Also, it is crucial to consider the downstream costs of additional testing, data collection, storage, analysis, interpretation, and follow-up of test results, including abortions (24,26,32,33,40,41). Moreover, the possible surge in NIPW use might increase financial burdens on the healthcare system and society (26) because of increased requests for genetic counselling, and overtreatment and medicalization of less severe conditions or non-medical traits (11,17,24,28). Chen and Wasserman deny the objections surrounding increased costs as a justification against implementing an unrestricted testing policy because they believe the

costs are necessary for responsible testing; they believe that additional costs are justifiable for the benefits that testing will proffer, but agree that from a public health perspective, it is logical to prioritize preventing more clinically severe conditions[2] (15). Thus, the cost effectiveness of NIPW needs to be assessed before it becomes clinically available (19,24,25).

Considering costs and funding of NIPW is necessary because in order to justify funding, the priority order of the screening technology must be discussed in relation to other goods and services (24,44). Allyse and colleagues state that the only way for an unrestricted policy on NIPW to work is if we live in a "frictionless healthcare setting in which all concerns of scientific limitation and resource allocation have been removed" (40, p.2). From a similar perspective, Ravitsky and others argue that funding decisions should be contingent on whether the testing technology is clinically highly accurate and translates into an enhanced reproductive decision-making, with the belief that even if this is the case, "there is no obligation to fund access […] to all available tests that may inform a reproductive decision, especially if the clinical significance of potential results is unclear" (32, p.40). Therefore, testing and counselling should be an out-of-pocket expense to avoid taking resources away from more urgent needs if parents wish to test for a wider set of conditions that are not medically indicated (32). There are claims that funding and investing resources into NIPW, especially unrestricted testing policies, would deprioritize and devalue other important public health goals and services that are more necessary and justifiable, such as universal pregnancy and neonatal care counselling and support (40). Authors agree that there should be reflection on how important it is to spend scarce resources on NIPW compared to other supports, conditions, and areas of healthcare to uphold the principle of distributive justice (25,27,44).

Limiting the scope of NIPW testing

The decision surrounding whether to fund NIPW requires determining the types of conditions that should be permitted for testing and which of those should be publicly funded. We previously discussed Chen and Wasserman's unrestricted testing policy proposal, which would include testing for any condition or trait that prospective parents believe is useful for reproductive decision-making (15). However, most agree that testing should be limited to conditions that have clinical significance and actionability, where the condition can be treated and prevented before birth or treated following birth (10,11,16,19,21,24,25,27,30,33,43). Chen and Wasserman believe that only restricting based on medical severity simplifies reproductive decision-making because it is not the only factor in deciding about testing and termination (15). Testing for late-onset diseases or susceptibility genes that are not immediately actionable in extreme circumstances, such as when there is no treatment available and termination is an option, has also been viewed as justifiable for the scope of testing (21,28), but not by all sources (24). There is also a high degree of uncertainty regarding the utility and significance of results (10,11,15,17,28), which may or may not be useful for parents to learn (24). Testing "for information only", without intentions to act on results, can also be justified because there may be medical benefits to managing pregnancy or birth (23). With the exception of Chen and Wasserman, there was little support in the literature we reviewed for including non-medical and other minor genetic traits in the scope of testing (15). Overall, it is evident that it will be difficult to agree on a set of conditions and variants that should be permitted for testing (40); nonetheless, determining the scope of testing is essential for policymaking surrounding NIPW.

Counselling, education, and support

If NIPW is to be implemented in clinical practice, there would need to be policies surrounding the level of counselling and support required for prospective parents as well as healthcare professionals who will offer this counselling. For instance, several authors advocate for a comprehensive pretest counselling process for prospective parents prior to undergoing NIPW so they are informed of harms and potential benefits of testing (10,15,19,21,24-26,28,36) to help facilitate informed decision-making. Educating prospective parents to ensure they are offered comprehensible information about NIPW and including a decision aid tool to explain the technology might support choices to accept or decline NIPW (10,15,24,25,28,36). Nonetheless, some authors argue that even with extensive counselling[3] it may still be difficult for parents to usefully apply the information from NIPW because of the vast amounts of information involved (32). When women were asked what sort of information they wished to receive from their NIPW results, almost half wanted clear recommendations and all options presented, and more than one-quarter wanted all options presented along with a joint decision-making process (38). This reveals that women find counselling and support from healthcare professionals helpful for making decisions following NIPW testing. The literature also recognizes that although genetic counsellors are best placed to counsel patients, there may be a shortage of counsellors (15,17,26), which needs to be considered before the test becomes accessible. One idea to overcome this shortage is to implement web-based or virtual interactive genetic counselling to reach large numbers of patients and to standardize the complex information NIPW offers to enhance understanding (15,26,28).

To ensure that parents receive counselling, support, and adequate information and education, healthcare professionals require proper education and training. Currently, healthcare professionals are not trained to discuss the complex information involved in NIPW because it is not yet used in practice. In one study, most obstetrician-gynecologists reported that they were

[2] There are variations in how "severity" is defined in the literature. Chen and Wasserman acknowledge that prospective parents would define mild, moderate, and severe conditions differently, and is thus a subjective classification (15). It can be defined based on quality of life of the future child or even the level of burden the condition would have on prospective parents. While some argue for more broad definitions of "severity", Munthe believes that severe conditions are those for which "no conceivable extent of societal adaptation or support will reduce the burdens to parents sufficiently to make access to (prenatal testing) into a mere luxury product" (43, p.44).

[3] The definition of "extensive counselling" and what this includes is not well-defined or discussed in the literature. Extensive counselling in this context should, we suggest, involve guidance from qualified healthcare professionals to help parents interpret NIPW results and discuss options that are in line with the values of the parents.

uncomfortable with the idea of communicating NIPW results to patients, preferred to refer patients to genetic counsellors, and believed that they would not have the necessary resources to interpret results (17). Professional societies can contribute to education and training on NIPW (10,26,41) along with medical education programs for healthcare professionals (35). Overall, additional training for clinicians on how to present and return genetic information that correlates with patient preferences is necessary (38). Part of the policies surrounding clinicians' education should also include developing guidance on how clinicians returning results should manage incidental findings[4] such as misattributed paternity (28) or findings that have health implications for parents or close relatives (11,19). Policies should therefore elaborate on what information should be returned, to whom, by whom, and when, and should reflect patient preferences (21,24,26). Further, such policies should discuss what information clinicians are responsible for interpreting, and how and whether data should be stored or reanalyzed when knowledge about variants of unknown significance become understood in the future, and whether patients should be recontacted (24).

DISCUSSION

This review provides an overview of the ethical, legal, social, and policy implications (ELSI) for the potential future use of non-invasive prenatal whole genome sequencing (NIPW). This research is useful to further understand the main implications of NIPW's clinical introduction and to shed light on the main stakeholders affected by this technology. It can thus inform and guide policy decisions for the future implementation of NIPW, including the main factors and arguments that need to be elucidated for effective and ethically sound policies. The literature shows that there are competing interests between two principal stakeholders: the future child and the prospective parents. These competing interests often translate into tensions over the same ethical concern. For instance, when exploring ethical issues surrounding autonomy, we notice that the literature discusses this with respect to the autonomy of future children and the autonomy of prospective parents, which are in conflict with each other. Several articles (10,16,18-21,27,28) explore how NIPW affects the autonomy rights of future children, including rights to an open future – whether as future children or adults – because they will be unable to choose whether to know or not know genetic information about themselves (e.g., late-onset diseases) that can influence their life course (16,18,20,21,24,25). While most authors agree that there is a risk to undermining the autonomy of future children, others argue that NIPW enhances parental autonomy because it can inform prospective parents' reproductive decision-making (15,25,27,28,30,33,46). The literature expressed further concern related to threats over informed consent caused by information overload from NIPW (10,15,16,18,19,24).

Based on our literature review, NIPW-related policy should elucidate how the autonomy of the future child should be weighed against the autonomy of the prospective parents to resolve conflicts over testing for a certain condition, which might in turn, be a challenging and arduous task given the vast amount and complexity of information generated by NIPW. Professional guidelines on genetic testing provide insights but are sometimes ambiguous regarding how to resolve conflicts over testing for certain conditions. For example, in its position on *Prenatal Testing for Adult-Onset Conditions*, the US National Society of Genetic Counselors recommends that conflicts "between the right of prospective parents to obtain information and the right of the future child should generally be resolved in favor of the parents" (47, p.1144). However, the American Committee of Obstetrics and Gynecology states, "In pregnancies likely to be carried to term, […] the decision to test should be reserved for the child to make upon reaching adulthood" (48, p.1498), and parental preferences should also be taken into account (48). In another joint statement with the Canadian College of Medical Geneticists, the Canadian Paediatric Society argues that "children should only be tested when it is for the purpose of better medical care" (49, p.42) and "for genetic conditions that will not present until adulthood [susceptibility or predictive testing], testing should be deferred until the child is competent to decide whether they want the information" (49, p.45). While recommendations by various professional societies might offer some guidance for clinical practice, a future NIPW policy should carefully address the clinical uses of NIPW, including the information that should or should not be offered to prospective parents.

In reviewing the social implications of NIPW, an interesting implication involved the changes in family dynamics. Several articles (10,17,21,23,28,29) discussed how the way parents treat their children would undoubtedly change based on what they learn from testing, even if subconsciously. The influences of these changes are difficult to measure because they are contingent on the type of information shared with parents, how the information is presented, how parents perceive the information, and how they choose to act or not act on the information when raising the child. This implication is important to understand because it can motivate research that would determine the kinds of information that might affect childrearing, which might in turn, inform policymaking.

In addition to changes to family dynamics, NIPW can lead to altered societal perceptions, including our ideas of what is "normal" and "healthy" (21,24,36,42). The literature discussed whether and how this technology would shape our understanding of human nature, which is important to anticipate and consider before implementing NIPW. Some sources (21,25,28) acknowledged that altered perceptions can include discrimination against conditions and traits that do not meet newly defined standards of "normal" or "healthy". While it is possible that Chen and Wasserman's unrestricted policy testing for all conditions can put all traits on equal ground and does not decide that one disease is worth testing over another (15), it will not stop negative societal perceptions towards the conditions, especially if more people are born without these undesirable traits. It is important to discuss how changes in societal perceptions towards select traits will affect individuals with those traits. For these

[4] Incidental findings are findings that are discovered and are outside the primary goals of the test, which in this case, would be relevant for NIPW (45). They also include testing results that prospective parents have not inquired about and can reveal clinically significant information.

reasons – and since persons living with disabilities as well as disability group advocates are critical stakeholders – their perceptions and voices must be included in discussions surrounding clinical introduction of NIPW.

The literature also explored several policy implications for NIPW implementation. For instance, several authors (10,15,19,21,24-26,28,36) agree that there should be improvements in supporting and counselling prospective parents to inform their decision-making, although fewer articles (10,26,35,38,41) addressed the need for education and training for healthcare professionals. The challenge in providing adequate information requires, on one hand, that healthcare professionals are trained, educated, and well-prepared for NIPW implementation, and on the other hand, that prospective parents understand the information provided to enhance informed decision-making. From that perspective, decision aid tools (e.g., websites) might be developed to facilitate parental decision-making that is congruent with their own values and preferences.

As with any technology, NIPW raises questions of funding and coverage by the healthcare system. Several sources (24,26,32,33,40,41) argued that the downstream costs of additional testing, including data collection, interpretation, and follow-up can burden the healthcare system. In addition, others discussed further burdens involved with overtreatment and medicalization of less severe conditions (e.g., non-medical conditions) that could result from implementation of NIPW, which has implications for cost distribution and how costs for NIPW might deprioritize other health concerns. Whether funding NIPW is contingent on the type of condition to be tested and whether there should be a limit on the scope of conditions to be tested are important considerations for discussions on cost and accessibility. However, since the literature shows a knowledge gap surrounding how to define the limitations – if any – on testing, more studies need to be conducted on how and whether policies should limit the scope of testing. Such studies can involve consultations with policymakers, persons living with disabilities, and disability rights advocates, among others, to learn more about their perceptions on what a future policy regarding NIPW coverage and testing should involve.

At a macro level, policies and regulations required for implementing NIPW can be developed either at governmental or nongovernmental levels. Some authors believe that regulatory interventions are not required at the government level (28,29) and rather should be regulated through professional societies and nonbinding guidance to uphold parental autonomy (29). In addition, Sullivan and colleagues showed that only about 15% of pregnant women agree that governments should decide on the categories of fetal genetic information that can and cannot be returned (38). However, for those who believe that NIPW should not yet be offered to pregnant women, governments would need to be involved in implementing a moratorium on testing (21). While guidance and regulations through professional societies are critical to guide healthcare professionals and prospective parents in using and implementing NIPW, governmental regulation of NIPW are also important, especially in countries like Canada where parental autonomy and reproductive choice are highly valued. Therefore, more research should be conducted on the types of regulations that could be introduced to allow for the ethically permissible implementation and use of NIPW.

LIMITATIONS

The use of a critical interpretive approach to conduct this review allowed for a comprehensive set of data spanning ten years in the literature on this topic, which might not have been so extensive in a more rigid search strategy. Including several electronic databases in the search helped to mitigate retrieval biases while a secondary manual search procedure limited source selection and publication biases. However, there are some limitations that should be acknowledged. While only English and French language articles were included, including studies from all countries helped somewhat to mitigate the possibility of selection biases. Since this was a critical interpretive literature review, there is a possibility of interpretation bias in which it can be difficult to objectively interpret and communicate findings from the literature; involving two interpreters partially mitigated this problem. Also, it is difficult to anticipate implications as well as draw conclusions from the literature considering the paucity of research on NIPW. The lack of empirical research assessing opinions and perspectives towards NIPW from key stakeholders indicates that critical voices are not included and therefore, evidence-based policies cannot yet be made. However, the technology is still evolving and it is important to review the theoretical literature on this subject before implementation. Our understanding of this technology will improve when it is introduced into clinical practice and more healthcare professionals and patients have lived experience with NIPW testing.

CONCLUSION

The implementation of NIPW in clinical practice offers several benefits, but raises challenges at the ethical, social, legal, and policy levels. Some perceived benefits include providing parents more time to plan for a child with special needs, upholding parental autonomy and the right to know, as well as the therapeutic benefits that might be potentially offered to the future child. Potential challenges include the anxiety and stress that can manifest for both parents and children, the threatened autonomy and right to an open future for the future child, information overload that undermines parental informed consent, concerns for informational privacy of the future child, and negative effects on parenting and treatment of children. Societal concerns of implementing NIPW include the potential for eugenic attitudes in society and discrimination against people with disability, increased rates of pregnancy termination for minor traits, altered societal perceptions of “healthy” and “normal”, and a societal pressure to use NIPW. Some policy recommendations include those that minimize cost and maximize priority of health resources, education for healthcare professionals, increased counselling and support for parents, minimizing disparities in access to testing, and limiting testing to certain conditions.

Table 2. Example of questions raised by NIPW

- Should parents have access to all the information NIPW provides?
  - If yes, based on what criteria?
  - If not, what information should they have access to and why?
- Who should decide on limiting or not limiting access to the information generated through NIPW? Governmental or nongovernmental (e.g., professional societies)?
- Should NIPW be covered by the healthcare system for specific conditions?
- How should social disparities (e.g., income, education) be addressed in test access and use?
- How should results be managed?
- How should incidental findings be managed?

While this review sheds light on various factors to be considered when discussing NIPW implementation, it shows that many questions are left unanswered (see Table 2) and thus there are many avenues for research to explore. As discussion surrounding NIPW is still in its infancy, it is of great importance that these concerns be addressed to allow for safe, fair, and ethical implementation into practice.

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