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# Non-invasive Prenatal Testing and the Unveiling of an Impaired Translation Process

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## Abstract

Non-invasive prenatal testing (NIPT) is an exciting technology with the potential to provide a variety of clinical benefits, including a reduction in miscarriages, via a decline in invasive testing. However, there is also concern that the economic and near-future clinical benefits of NIPT have been overstated and the potential limitations and harms underplayed. NIPT, therefore, presents an opportunity to explore the ways in which a range of social pressures and policies can influence the translation, implementation, and use of a health care innovation. NIPT is often framed as a potential first tier screen that should be offered to all pregnant women, despite concerns over cost-effectiveness. Multiple forces have contributed to a problematic translational environment in Canada, creating pressure towards first tier implementation. Governments have contributed to commercialization pressure by framing the publicly funded research sector as a potential engine of economic growth. Members of industry have an incentive to frame clinical value as beneficial to the broadest possible cohort in order to maximize market size. Many studies of NIPT were directly funded and performed by private

industry in laboratories lacking strong independent oversight. Physicians' fear of potential liability for failing to recommend NIPT may further drive widespread uptake. Broad social endorsement, when combined with these translation pressures, could result in the "routinization" of NIPT, thereby adversely affecting women's reproductive autonomy. Policymakers should demand robust independent evidence of clinical and public health utility relevant to their respective jurisdictions before making decisions regarding public funding for NIPT.

## Résumé

Le dépistage prénatal non effractif (DPNE) est une technologie remarquable ayant le potentiel d'offrir une multitude d'avantages cliniques, notamment une réduction des fausses couches, grâce à la diminution du nombre d'examen invasifs. Cependant, certains soupçonnent que les avantages économiques et cliniques à court terme du DPNE ont été surévalués, et ses limites et méfaits, minimisés. Il y a donc lieu d'étudier de quelle façon les pressions sociales et les politiques influencent l'application concrète, la mise en œuvre et l'utilisation d'innovations en soins de santé comme le DPNE. Malgré les réserves quant à son rapport coût-efficacité, le DPNE est souvent présenté comme un premier palier d'examen qui devrait être offert à toutes les femmes enceintes. De nombreux facteurs ont contribué à un environnement translationnel problématique au Canada, poussant à l'adoption de cette technologie comme premier palier d'examen. Les gouvernements ont exercé des pressions pour qu'on commercialise le DPNE, en présentant le secteur de la recherche financée par les deniers publics comme un possible moteur de croissance

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économique. Afin d'optimiser la taille de leur marché, les acteurs du secteur ont tout avantage à défendre la valeur clinique de cette technologie pour en vanter les bienfaits pour le plus grand nombre de personnes possible. Nombre d'études sur le DPNE ont été réalisées et financées directement par le secteur privé dans des laboratoires sans supervision indépendante adéquate. Par ailleurs, la crainte pour les médecins d'être tenus responsables s'ils ne recommandent pas un DPNE à leurs patientes peut aussi provoquer l'adoption généralisée de la procédure. Combinée à ces pressions de mise en application, la forte adhésion sociale pourrait mener à une « systématisation » du DPNE et, par conséquent, nuire à l'autodétermination reproductive des femmes. C'est pourquoi les décideurs devraient, avant de prendre des décisions relativement au financement public du DPNE, exiger des preuves solides et indépendantes sur sa pertinence clinique et sanitaire dans leur province ou leur territoire.

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## CONTEXT

The development and potential clinical application of non-invasive prenatal testing (NIPT) have generated an increasing amount of attention in the scientific and health care communities,<sup>1,2</sup> in the media,<sup>3,4</sup> and among policymakers.<sup>5–7</sup> NIPT is an exciting technology with the potential to provide a variety of clinical benefits, including a reduction in the number of women undergoing amniocentesis and chorionic villus sampling and, consequently, a reduction in the number of miscarriages and related health effects caused by invasive procedures.<sup>8,9</sup> Some have suggested that the introduction of NIPT could reduce health care costs and enhance reproductive autonomy by broadening women's choices.<sup>10</sup> However, there is also concern that the economic and near-future clinical benefits have been overstated and the potential limitations and harms underplayed.<sup>11–13</sup> Indeed, multiple forces have created a less than ideal translational environment, one that may be creating pressure to implement NIPT prematurely and utilize it in a manner that is not supported by the best available evidence.<sup>14–16</sup>

NIPT was developed as a commercial screening test in the United States after the discovery that trace quantities of placental DNA are present in the bloodstream of a pregnant woman; placental DNA is largely composed of DNA also shared by the fetus, although this is not the case in confined placental mosaicism.<sup>17,18</sup> NIPT screens for aneuploidies such as trisomy 21 (Down syndrome), trisomy 18, trisomy 13, and other chromosome number abnormalities, without increasing the risk of miscarriage and with

a higher reliability than many current screening tests. However, confirmation of the results using amniocentesis or chorionic villus sampling is required. In Canada, there have been recommendations to publicly fund NIPT.<sup>19</sup> Currently, British Columbia and Ontario have approved funding of NIPT as a second tier screening test—that is, a test for women who have already been identified as having a high-risk pregnancy.<sup>20,21</sup> Professional societies such as the Society of Obstetricians and Gynaecologists of Canada concur with this usage.<sup>22</sup> However, some companies that sell NIPT, as well as some commentators and researchers, have suggested that it should be provided as a first tier screen for all pregnant women, regardless of risk profile.<sup>23–26</sup> Most NIPT currently performed in Canada is provided by companies based in the United States.

Important discussions about the true value of NIPT for couples, health systems, and the public are ongoing.<sup>5,8,11,12</sup> Existing innovation policies and market forces have had an impact on the presentation, adoption, and clinical utilization of NIPT. For example, some have speculated that commercialization pressures may have an impact on the representation and translation of emerging technologies,<sup>27</sup> and that existing patents have already shaped the utilization of NIPT, at least in the United States.<sup>28</sup>

NIPT, therefore, presents an opportunity to explore the ways in which a range of social pressures and policies can influence the translation, implementation, and use of a health care innovation. Here, we discuss the pressures that shape how NIPT is being adopted and funded in Canada and provide recommendations for what needs to change to promote an evidence-based approach that will benefit both Canadians and their public health care systems.

## ASSESSING THE BENEFITS

NIPT is undoubtedly an exciting clinical development, and its effect of reducing the number of invasive procedures is already being felt by the health systems in which it has been implemented. However, independent assessments of this technology have consistently identified reasons to ask for stronger and independent evidence to support some of the claimed benefits. For example, NIPT is increasingly being framed as a possible first tier screen that should be offered to all pregnant women,<sup>23,29,30</sup> while several scientific societies and health technology assessments have argued against such a use because of the lack of unbiased and clear evidence that first tier NIPT would be a good use of health care funding.<sup>31–33</sup> Independent assessments of NIPT have concluded that although there is a high risk of bias in

published estimates of its performance, it is likely to be an effective second tier screening approach.<sup>31–33</sup>

Additionally, these same independent assessments agree that validated diagnostic techniques such as amniocentesis are required to confirm an abnormal NIPT result.<sup>31–33</sup> Indeed, when NIPT is used as a screen for high-risk women, recent review data show that the positive predictive value for Down syndrome, the condition most commonly screened for, is approximately 91%.<sup>32</sup> Other identified limitations of NIPT include possible discordance with the fetal karyotype, lower efficacy for detecting trisomy 13 (87%), trisomy 18 (84%), and X chromosome disequilibrium than for detecting trisomy 21, limited data on use with twin pregnancies, and high cost.<sup>32,34</sup> Indeed, clear explanation and understanding of the limitations of NIPT are necessary to ensure appropriate informed consent of women as recommended by current NIPT guidelines. However, appropriate counselling about genetics, test performance, test limitations, and the potential for unanticipated information (such as maternal cancer, fetal sex, or other fetal genetic abnormalities such as large chromosome deletions or duplications) significantly burdens the clinical infrastructures of family physicians, obstetricians, and gynaecologists. This burden contributes to a significant risk that women will underestimate the limitations and risks of NIPT.<sup>35,36</sup>

From a health economics perspective, the costs associated with use of NIPT as a first tier screen would be very different from those associated with using it only among women at high risk. In the latter population, it has been demonstrated to be cost-neutral or to reduce costs by reducing invasive testing.<sup>5</sup> Okun et al. projected the costs of using NIPT as a first tier screen in Ontario and compared these to the current costs of use as a second tier screen.<sup>9</sup> They found that first tier implementation would increase costs by a factor of 4.9; in real terms, costs would increase from approximately \$17.35 million to over \$85.14 million.<sup>9</sup> Moreover, since the majority of diagnoses of fetal Down syndrome are in women already identified as being at high risk, the estimated cost per additional diagnosis of Down syndrome was \$472 139.<sup>9</sup> These projections are generally consistent with findings in the United Kingdom and Belgium that first tier implementation is currently unjustifiable because of additional cost.<sup>37,38</sup> However, a recent analysis published by a major private provider of NIPT found it to be cost effective in the United States as a first tier screen.<sup>39</sup> Nonetheless, there is reason to doubt claims that the first tier use of NIPT in its current form will reduce overall health care costs.<sup>10,32</sup>

Problems with economic analyses of NIPT include controversy about how to evaluate the economic outcomes of preventing an abnormal birth and the inability to standardize the benefit of NIPT with measures such as quality-adjusted life years for the purpose of allocating resources and maximizing public benefit.<sup>40,41</sup> Specifically, ethical concerns arise because the lives of individuals with Down syndrome are often assigned no value, but full consideration is given to the additional costs associated with their care and education.

## **TRANSLATION PRESSURES**

### **Commercialization Pressures**

Over the past decade, governments throughout the world have increasingly turned to the publicly funded research sector as an engine of economic growth. In Canada, for example, this ethos has permeated every aspect of research funding.<sup>15,27,42</sup> Much of the commercialization and innovation surrounding NIPT has occurred in the United States, where these pressures are as intense as in Canada and possibly more so.<sup>28</sup> There is a growing body of evidence indicating that commercialization pressures and ties with industry can have a significant biasing effect on research outcomes and representations, such as increasing the likelihood that benefits will be overstated.<sup>43–52</sup>

The adverse impact of pressure to commercialize may be amplified by inappropriately narrow policy definitions or perceptions of research benefit, such as a focus on patentable inventions rather than broader benefits to society. For instance, some have used the number of patents filed in a given period as a metric for the success of national innovation policy.<sup>53</sup> However, this is a poor proxy, as patents do not in themselves necessarily indicate the existence of socially beneficial inventions, or even successful commercialization activity<sup>54</sup>—a reality that has been noted by university technology transfer offices.<sup>55</sup> Given the pervasive and well-documented influence of these pressures, it is reasonable to assume that they have helped to shape how NIPT has been represented and implemented in the Canadian health care system.

This seems particularly true when one considers the sizable market for NIPT.<sup>28,56</sup> Although projections change over time, there is no doubt that the potential worldwide net market worth of NIPT is measured in billions of dollars.<sup>57–59</sup> This creates a substantial incentive to capture market share and to frame clinical value as beneficial to the broadest possible cohort—the more potential users, the larger the potential market. As a result, companies selling NIPT lobby for its use as a first

tier screen for all pregnant women in order to increase market size.<sup>60</sup> Some companies have also begun to develop NIPT that screens for a higher number of conditions than clinically justifiable, with the eventual goal of mapping the entire fetal genome.<sup>61–64</sup> These initiatives can help companies appear to offer a superior product, allowing them to maintain high prices and profits as the existing basic screens become more widely adopted and less expensive.

Market pressures may also have caused the predictive value of NIPT to be overestimated.<sup>43,44,65–67</sup> Many major studies of NIPT were directly funded and performed by private industry.<sup>23,68–71</sup> As such, much of the research was done in private laboratories. Some suggest that such laboratories lack sufficient independent oversight, which allows issues of bias or non-proficiency to be overlooked.<sup>72</sup> Indeed, two recent meta-analyses show that the methodological quality of most published NIPT studies is limited.<sup>31,32,73</sup> Issues include small sample size, risk of biases, and potential inapplicability of existing research to NIPT's use as a screening test for the general population.<sup>31,32,73</sup> Corporate involvement contributes to the bias towards increased performance, that, when combined with confusing language about specificity, sensitivity, and positive predictive value, can manipulate consumers.<sup>74</sup> This is particularly problematic because of the relative absence of independent sources of information for women and couples regarding NIPT and its performance.

Although it is expected that manufacturers will initially produce validation data for their products, independent confirmation of test performances and utility are an important step towards recognition of a test's value in improving patient outcomes. However, a manufacturer's ownership of a patent can significantly hinder independent validation by restricting access to technologies and increasing costs;<sup>75</sup> this in part explains why robust independent confirmation for some applications of NIPT is lacking.

Moreover, pressure to translate and commercialize may also lead to exaggerated or hyped popular representations of new technologies.<sup>76</sup> This is a phenomenon that has occurred in other domains, such as stem cell research and genetics.<sup>77–79</sup> This hype compounds and further shapes representations of research and the process of translation by enabling an inappropriate push towards premature clinical translation.<sup>15</sup> This may be one reason why NIPT is currently being presented as a possible first tier solution for average-risk women,<sup>80</sup> even though solid, independent evidence regarding its effectiveness in this context is still lacking.

### Public Perceptions and Patients' Attitudes

NIPT is emerging at a time when interest in prenatal genetic information is growing.<sup>62,81,82</sup> Since NIPT was introduced into clinical use, several studies have been published assessing stakeholders' opinions and attitudes towards it. A recent literature review identified no less than 10 publications reporting attitudes towards hypothetical future uses of NIPT and five reporting evidence from clinical practice.<sup>83</sup> A few key findings emerge from these studies. While attitudes of all stakeholders are consistently positive overall, important differences in opinion have been observed between users (pregnant women) and health professionals.<sup>6</sup> Improved safety (i.e., absence of an increased risk of miscarriage) compared with invasive methods is the most important factor increasing favourability among women,<sup>1</sup> and improved performance compared with current screening methods is the most important factor for health care providers.<sup>7,84</sup>

Overall, the main perceived benefits of NIPT are increased safety (compared with invasive tests), ease of use, accuracy, and availability early in pregnancy.<sup>85</sup> Interestingly, the most common concerns are directly linked to these advantages. Because NIPT is "easy," there is concern that pregnant women may not appreciate the range of implications potentially indicated by a positive result. In addition, women and families could feel increased pressure to be screened and possibly even to terminate a pregnancy found to be trisomic or to have another condition, thereby undermining their autonomy to make an informed decision. These research results point to the need for appropriate pre- and post-screen counselling, which appears to have been implemented in the United Kingdom.<sup>85</sup>

Interestingly, evidence also indicates that pregnant women do not necessarily feel that "more information is better" in prenatal testing. Indeed, a survey of 2666 women by Minear et al. found that the majority of the women believed that NIPT's safety was more important than its information content.<sup>6</sup> In another study, nearly 40% of 381 Dutch women surveyed felt that more information from NIPT could force couples to make more difficult choices.<sup>86</sup> Perspectives presented in the media and in academic forums can stoke concerns about the potential societal consequences of using NIPT now and in the future to favour certain genetic constitutions.<sup>87</sup> Some have even claimed that state-sponsored use of NIPT is promoting eugenic social attitudes or could potentially promote them.<sup>88–90</sup>

### LEGAL PRESSURE

Risk of liability can also act as a translation pressure. Physicians' legal obligation to uphold a standard of care

when interacting with their patients requires disclosure of all relevant alternative tests and treatments. The fear of potential liability for failing to recommend NIPT may further drive uptake.<sup>91</sup> In this way, existing legal norms could facilitate broader adoption of NIPT. Indeed, research has consistently found that legal norms can drive utilization patterns, usually in the direction of offering patients more testing.<sup>91</sup>

### Framing NIPT as a Routine Part of Care

The way in which NIPT is framed as an emerging technology will shape public and patient expectations, and their perceptions of risks and benefits. Evidence already indicates that NIPT is widely viewed as a positive development in prenatal care.<sup>1,92,93</sup> The fact that informational resources for women and health care providers are almost exclusively produced and disseminated by the companies that sell NIPT contributes to positive perceptions. Moreover, public representations of NIPT in the popular press, which are predominantly favourable, are largely framed from the perspective of industry.<sup>4,94–96</sup>

Broad social endorsement, when combined with translation pressures, could result in the “routinization” of NIPT; this would adversely affect women’s reproductive autonomy because they would feel pressured to undergo such a widely endorsed option.<sup>97,98</sup> It is even possible that screening with NIPT could become akin to prenatal ultrasound assessment, for which informed consent is practically non-existent; such assessment is performed with little or no prior discussion or counselling because of widespread use and the absence of an increased risk of miscarriage.<sup>83,99</sup> Survey evidence already indicates that care providers view informed consent for NIPT as less important than for invasive testing because of the absence of direct risk to the fetus.<sup>100</sup>

### TOWARDS RESPONSIBLE GOVERNANCE OF NIPT AND RELATED TECHNOLOGIES

NIPT exemplifies how policy discussion about a valuable technology can be affected by various uncoordinated translation pressures to produce a less than ideal public discourse and implementation. Commercialization and translation pressures have clearly affected the framing of the technology’s implementation. These pressures are pushing towards broad and pervasive application of NIPT. Legal norms governing the physician-patient relationship, and concern about liability, may have also contributed to a push for adoption. Finally, pressure from patients has been multifaceted, as the majority support a technology that can reduce the number of miscarriages and common

**Figure. Important steps for future policymaking**

- |     |  |
|-----|--|
| (1) | Assessment of corporate biases and conflicts of interest             |
| (2) | Independent validation of technology performance                     |
| (3) | Consideration of all stakeholder perspectives                        |
| (4) | Standardized assessment of economic performance                      |
| (5) | Assessment of overall effectiveness in achieving public health goals |

aneuploidies through identification and early pregnancy termination, but many are wary of the ethical challenges that would accompany NIPT’s pervasive application.

The result of these pressures has been fast adoption in the absence of both robust independent data and independently produced informational materials as well as a strong push towards pervasive first tier screening with NIPT despite its possible cost ineffectiveness, its high opportunity costs, and a lack of evidence of substantial public health benefit beyond second tier models. Policymakers should demand robust independent evidence of clinical and public health utility relevant to their respective jurisdictions before making decisions regarding public funding for NIPT (Figure).

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