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OBM Genetics

Opinion

Moving Towards Routine Non-Invasive Prenatal Testing (NIPT): Challenges Related to Women's Autonomy

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Academic Editors: Joanne Traeger-Synodinos and François Rousseau

Special Issue: Genetic Screening

OBM Genetics
2018, volume 2, issue 2
doi:10.21926/obm.genet.1802018

Received: February 10, 2018
Accepted: March 19, 2018
Published: April 20, 2018

Abstract:
Women's reproductive autonomy, and its translation into informed free choice regarding prenatal screening, is a dominant concept in the bioethical discourse concerning prenatal screening. This discourse is based on the premise that access to information regarding the pregnancy promotes autonomous decision-making. However, studies show that the offer of prenatal screening as a routine part of pregnancy care is not supported, to a large degree, by appropriate informed consent mechanisms. This means that the implementation of the concept of autonomy faces significant challenges. On the backdrop of these ongoing challenges, the introduction of Non-Invasive Prenatal Testing (NIPT) offers numerous benefits for pregnant women. The main advantages of NIPT are early availability of results, non-invasiveness and absence of risk for the fetus, as well as increased accuracy compared with earlier screening

technologies. These advantages may lead to routinization of the test, which will have the advantage of facilitated access to the test. However, such routinization also raises unique issues and challenges regarding the respect of women's autonomous decision-making. To shed light on the developments in the implementation of NIPT, this paper presents some longstanding ethical concerns regarding prenatal screening and examines what makes NIPT different from earlier screening technologies. It also charts possible future uses of NIPT, such as first-tier screening, diagnosis, expanded targeted use, and whole-genome sequencing, while anticipating the ethical and social implications of the various signposts potentially encountered, particularly as they relate to reproductive autonomy.

Keywords
NIPT; prenatal screening; prenatal test; autonomy; informed consent

1. Introduction

Innovation in prenatal screening re-opens and re-frames old ethical debates in this area [1]. Since the introduction of amniocentesis in the mid-20th century, questions surrounding access to prenatal genetic information and its effect on society have been raised [2]. However, the translation and implementation processes for such prenatal testing technologies have encouraged broad uptake before their clinical, ethical and social ramifications have been thoroughly considered [3, 4]. Therefore, as cell-free fetal DNA, or non-invasive prenatal testing (NIPT), gradually establishes itself, with the potential to perhaps someday completely replace traditional methods of screening, it is essential to reassess classic ethical and social debates in view of the technology's new clinical attributes. This paper briefly presents some longstanding ethical concerns regarding prenatal screening, examines what makes NIPT different from earlier screening technologies, and charts the possible future courses of NIPT while anticipating the ethical and social implications of the various signposts potentially encountered, particularly as they relate to reproductive autonomy.

Prenatal screening refers to any technology that identifies pregnancies with a high probability of being affected with a certain condition. Prenatal screening differs from prenatal diagnosis in that screening only yields probabilistic result such as 1:100, 1:10 000, and thus never completely rules out the possibility of the disease or condition being present. Diagnostic tests do provide a definitive positive or negative result. A diagnostic procedure is thus needed to confirm screening results before deciding on a further course of action (e.g., preparation for a child with possible special needs, prenatal intervention, or pregnancy termination).

Non-invasive prenatal screening has had considerable success internationally since its introduction in 2011 [5]. It is already being offered as a second-tier screening test for high risk pregnancies under public insurance in some Canadian provinces (e.g., Ontario and British Columbia) [6, 7]. NIPT is based on the finding that cell-free fetal DNA (originating in the placenta) is circulating in pregnant women's plasma in quantities sufficient for performing genetic testing. What distinguishes NIPT from

previously available prenatal screening technologies is the fact that it can be performed earlier in the pregnancy (as early as week 10) and that the results are more accurate [8, 9].

The fact that results can be available earlier provides parents more time to make decisions about the course of action and outcome of the pregnancy. Likewise, NIPT's improved accuracy reduces the number of false-positive and false-negative results thereby diminishing the drawbacks associated with traditional modes of screening. False-negative results can generate a false sense of reassurance, while false-positive results can provoke unnecessary anxiety and stress. NIPT also reduces the need for invasive procedures since it has higher detection rates and lower false-positive rates compared to any previous prenatal screening tests. NIPT thus has the great benefit of reducing the number of fetal losses associated with invasive tests. When it comes to a positive NIPT result, professional societies recommend confirming the result with invasive diagnostic testing prior to making any decision regarding termination [7].

The benefits NIPT may offer pregnant women are significant, and therefore, not offering it may constitute an infringement on reproductive autonomy. However, it is precisely these purported benefits of NIPT that ethicists warn may lead to an exacerbation of some ethical issues associated with prenatal testing. While the benefits of NIPT are evident, this paper focuses on these less obvious implications of NIPT for reproductive autonomy.

2. Longstanding Issues Raised by Prenatal Screening

At its inception in the 60's and 70's, prenatal screening was presented as a means of preventing disease and "mental retardation" [10]. It is only in the 90's that the concept of reproductive autonomy became dominant in the discourse concerning prenatal screening. Following criticism from feminist and disability rights activists, the various professional bodies involved in providing prenatal screening services distanced themselves from accusations of eugenic practices by framing prenatal screening as a matter of personal choice regarding one's life as opposed to a matter of public health [10].

Since then, autonomy and choice have been heralded as the main goals of prenatal screening [11], fitting into 'free-market' narratives that medical innovations are adopted as a result of sufficient demand by free and rational homo oeconomicus [12]. This would mean that women of child-bearing age must have demonstrated sufficient interest for market forces to drive the development of relevant tests. However, in the case of prenatal screening, this scenario has been questioned: "programs were initiated by government organizations, interested sectors of the medical profession, and the medical supply industry for their own purposes" [11, 13]. This strengthens the argument that autonomy might be used as a fig leaf hiding different interests [14].

Paradoxically, while being touted as enhancing choice, prenatal screening has, from its infancy, been criticized for undermining parents' autonomy [4]. Press and Browner claimed that when screening programs were first introduced by the government (in their case, in California), stakeholders had no interest in promoting reproductive autonomy via processes of informed consent. Stakeholders included the attending healthcare professionals who feared that if women reject screening they may face malpractice liability for "later claims of inadequate test explanation," policy-

makers whose interests were in increasing screening for economic and public health reasons, and expecting women who wanted access to available services but preferred to not engage in complicated deliberations that would involve the possibility of pregnancy termination. It is therefore important to contextualize the concept of "choice" that allegedly underlies prenatal screening within the broader social context, in order to effectively frame these choices (or lack thereof). Prenatal screening has thus been criticized for raising a slew of issues that ultimately inhibit reproductive autonomy, precisely the opposite of what it was lauded for.

2.1. Effects of Societal Pressures on Reproductive Autonomy

Societal pressure to screen, to diagnose or to terminate a pregnancy in case of positive results negatively affects the possibility of exercising reproductive autonomy. These are three separate, but interconnected, pressures. It is argued that, given the nature of our "performance society" [15], prenatal screening for conditions perceived as disabilities is framed as the responsible choice. As such, pregnant women often feel obligated to screen for these conditions and accede to the "collective silence" that positive results should eventually lead to pregnancy termination [16]. Many people, when faced with the decision of whether to pursue prenatal screening, may believe that it would be irresponsible to decline participation in a publicly funded program seemingly designed for the benefit of society as a whole. After all, the implementation of such tests by the medical system "establishes screening as a legitimate use of scarce medical resources and thereby surreptitiously underlin[es] its importance" [11].

Pressures from the medical community also exacerbate the onus felt by parents to screen prenatally. There is evidence that medicine and preventive care are playing an increasing role in influencing decisions related to personal and social life. Great importance is placed on early detection and prevention of diseases and conditions, which has resulted in societal beliefs that people should participate in prevention programs and can be "morally blamed" if they fail to do so [17]. Pregnancy, essentially a personal life event, has been affected by this social emphasis on disease prevention and is often perceived as requiring medical intervention and preventive care.

Furthermore, clinicians are often criticized for being too directive when counselling patients regarding prenatal screening options [16]. Logistical constraints, fears of malpractice and negligence litigation as well as clinicians' own perceptions of the value of screening are all factors that can lead to clinicians – consciously or unconsciously – placing undue pressure on women to undergo prenatal screening. Likewise, when discussing possible future results of screening, high-risk results are often framed in ways that do not allow much space for deciding not to continue on the testing pathway. When results become available, problems in communicating them clearly, transparently, meaningfully, and in a non-directive manner have been documented, with practitioners more often recommending screening, diagnosis and pregnancy termination [18-20].

Lippman noted as early as 1986 that "implicit in the model is the acceptance […] that women whose fetuses are found to be affected will abort the pregnancy, since for most of the conditions for which screening can be done there is, at present, no treatment" in utero [21]. Indeed, until today, the vast majority of pregnancies found to be affected with Down syndrome are terminated [22]. The lack

of social support for those raising children with special needs is thought to contribute to this sense of limited choice: "without extensive social support systems, termination may be the only viable reproductive option even when women or families may be willing or may desire to raise a child with special needs" [23].

Intimately related to the pressure to terminate are the so-called eugenics concerns, or what is often referred to as the "disability critique" of prenatal screening. The disability critique claims that not only does the elimination of persons with certain conditions lead to further stigmatization of the condition, but that such practices may affect individuals already living with the condition. As such, if there is a decrease in the birth rate of individuals with a particular condition, the number of public resources and support services may also decrease [24]. In attempting to enhance reproductive autonomy, it is important not to decrease the choices available to those who may want to pursue a pregnancy diagnosed with a disability or condition.

2.2. Reproductive Autonomy and Informed Choice

In addition to feeling undue pressure when presented with the allegedly free choice of whether to screen, diagnose, and terminate, infringements on reproductive autonomy can occur when women do not sufficiently understand the implications of the test. Research has revealed that a significant number of women undergo screening without being aware that they were being tested [25, 26]. Even if they are made aware that they are being screened and agree to it, many women report having received inadequate information about the conditions screened for, and what these conditions imply on a day-to-day basis, or having been led to believe that screening was mandatory or medically required [27-30]. Such practices reflect the lack of time allowed for counseling: "As almost all results will be reassuring, professionals may also find it less important to inform women about the choices they may be faced with down the line of a further screening trajectory" [31].

Disability rights scholars and activists claim that many people make prenatal screening decisions based on misconceptions about disability [24], therefore making uninformed choices, and that these misconceptions may be reinforced by health professionals who share them [32]. Accordingly, the disability rights critique has been making use of the language of informed choice in articulating its charges against current practices of prenatal screening [24, 33].

Even if all relevant information regarding screening is made available and precautions to avoid any undue pressure are taken, the question regarding whether more information necessarily translates into greater autonomy remains. Evidence shows that prospective parents may experience bewilderment at the amount of information provided by prenatal screening [18]. Information overload can be a cause of anxiety and stress and prospective parents may be left feeling perplexed when faced with the subsequent decisions they must make. It is important to note that this "burden of choice imposed on women" [34] is difficult because of the sensitive nature of the information presented. This type of information can unnecessarily increase anxiety for the prospective parents [35], negatively affect the pregnancy experience and present parents with difficult reproductive choices – choices that they might not have had to face if they had forgone prenatal screening [31, 36].

Additionally, this "bewilderment" applies not only to results provided *by* prenatal screening but also to information provided *about* prenatal screening at various stages of the process. Hence, while Press and Browner [4] pointed out that prospective parents prefer not to dwell on the social and ethical dimensions of prenatal screening, Kukla [37] suggested that parents often make a conscious choice to defer decisions to healthcare practitioners as a way of avoiding the burdens of information overload and decision-making regarding screening.

While respecting autonomy necessarily requires doing so throughout the process of prenatal screening, the social contexts outlined above create barriers to achieving this goal [14]. Seavilleklein [11] concludes that "there is incontrovertible evidence that women are not making free informed choices about prenatal screening", that "whether choice is interpreted narrowly as informed consent or broadly as relational, there are reasons to worry that women's autonomy is not being protected or promoted by the routine offer of screening" and that "incorporating the offer of prenatal screening into routine prenatal care for all pregnant women is not supported by the value of autonomy and ought to be reconsidered." These conclusions regarding prenatal screening were reached before the advent of NIPT. Ultimately, the introduction of any new prenatal screening technology into mainstream practice would require an attentive assessment of whether its implementation would contribute to or conversely undermine reproductive autonomy.

3. How NIPT Affects the Ethics Landscape

Prenatal screening is seen by many women as part of routine prenatal care [38]. Although NIPT has been rapidly implemented into publicly-funded screening pathways in some countries (e.g. the Netherlands, Belgium) [39-41], in most countries it is still offered only privately [5, 23] and is not yet considered standard of care, despite strong commercial interests that strive to make it a routine part of prenatal care [3, 24]. NIPT offers great benefits and is thus a laudable, as well as ethically acceptable, step forward when it comes to enhancing women's access to information they desire. At the same time, issues inherent in prenatal screening concerning reproductive autonomy have not yet been resolved and can now be exacerbated by NIPT.

First, NIPT can provide results earlier in the pregnancy than previous screening tests. This provides a crucial benefit to pregnant women and their families, as it allows earlier diagnostic testing and – in case of a positive diagnostic result – either more time to prepare for possible early therapeutic interventions or just to prepare for the birth of a child with special needs, or an earlier pregnancy termination. At the same time, the timing, reliability and safe nature of NIPT exacerbate concerns regarding the pressure placed on parents to screen and possibly terminate due to positive diagnostic results. Prior to the introduction of NIPT, parents could decline screening under the 'pretext' of poor performance of conventional screens, the risk of miscarriage associated with invasive diagnostic testing and the fact that results are only available at an advanced stage of the pregnancy (approaching 20 weeks) even if they actually had other reasons for not screening [42]. Such reasons could include a preference for a less medicalized pregnancy or an acceptance of the possibility of having a disabled child, reasons which they might fear care providers, family members or society would not approve of [43].

Second, the non-invasive (i.e. safe for the fetus) nature of NIPT, may lead to further undermining of informed consent and reproductive autonomy. Empirical studies have shown that some healthcare professionals believe NIPT warrants less formal informed consent procedures because it presents no increased risk of miscarriage [44, 45]. In addition, the common practice of same day pre-test counselling, directly followed by NIPT, further erodes informed consent because it eliminates the reflection period during which patients can discuss and decide whether to undergo screening [34].

Third, the increased accuracy of NIPT results, as compared with previous screening techniques, changes the nature of the information the test yields. Whereas previous technologies provided a probability that the pregnancy is at high risk, NIPT now yields results (at least for trisomy 21) that may be perceived by parents as quasi-diagnostic. If consent is lacking or not fully informed, parents may receive results that they are unprepared for, or even do not wish to know. It may be argued that disclosure of an unwanted from NIPT result that is more reliable violates parents' reproductive autonomy more extensively than the disclosure of more uncertain risk information [14].

On the other hand, some may view the disclosure of more reliable results, even without appropriate consent, as less damaging than the disclosure of risk information. This is because risk information can create much anxiety for no reason (since with previous screening technologies most cases ended up being false positives), whereas NIPT results provide more certainty and significantly reduce the number of individuals unnecessarily exposed to anxiety and stress. This is the rationale behind the recently proposed mechanism of 'reflex testing' [46], in which two blood samples are taken when women go through conventional serum screening. If a woman's first-tier screen comes back as high-risk, her second blood sample is automatically sent for NIPT, and the woman is only informed of the NIPT result, without ever having been exposed to the less reliable result of the first-tier screen. The researchers who proposed this model argue that this eliminates the unnecessary anxiety suffered by all those for whom first-tier serum screening produces false-positive high-risk results. However, there is no assurance of women being properly counseled and understanding the testing pathway they have unknowingly embarked upon. Thus, the advantage of reduced anxiety is achieved at the expense of informed consent and the woman's right to choose [47-49].

4. NIPT's Future Expansion

4.1. NIPT as First-Tier Screening

As recently as 2015, Dondorp et al. stated that the introduction of NIPT "lead[ing] to abandoning two-step screening" was "unrealistic" [31]. This statement is proving to be premature since there seems to be a shift in policies and standards adopted by different jurisdictions, recommending the use of NIPT as a first-tier screen. For instance, in 2015 and 2016, the Society for Maternal Fetal Medicine (SMFM), the American Congress of Obstetricians and Gynecologists (ACOG), the American College of Medical Genetics and Genomics (ACMG) and the International Society for Prenatal Diagnosis (ISPD) all modified their positions on NIPT in favour of making the technology available to all pregnant women, regardless of their risk status [50-52]. Likewise, more recently in 2017, the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Canadian College of Medical

Genetics (CCMG) released a joint guideline stating that NIPT can be offered as an option to all pregnant women provided that they understand it may not be provincially funded [7].

However, the risks NIPT poses to reproductive autonomy as a first-tier screening test are substantial. If NIPT becomes an option available to the general population of pregnant women and not only to those considered at high-risk, this will have an important impact on the current medical practices of general health practitioners, who are rarely specialized in the area of genetics. Onus will fall on front-line healthcare providers to discuss screening and testing options, along with communicating NIPT results [53], even though it is possible that they may not fully understand neither the complexity of the genetic results nor the evolving prenatal screening options.

This is further complicated by the fact that health care providers may believe informed consent is even less important when using NIPT compared with diagnostic tests [45]. The emerging scenario of NIPT as first-tier screening may mean that, in reality, reproductive autonomy will be more difficult to protect through informed consent. This highlights the importance of policies aiming to reduce the stigma associated with having children with special needs and ensuring that resources are in place to support any reproductive decision women and families make [14, 54].

4.2. Non-Invasive Prenatal Diagnosis ("NIPD")

If NIPT is further expanded to become a diagnostic tool, replacing classic diagnostic techniques such as amniocentesis, this could further exacerbate autonomy-related concerns, since women and their partners, as noted above, would no longer be able to use the risk of miscarriage as a reason to reject testing. NIPT is currently used as diagnostic for achondroplasia and thanatophoric dysplasia [55], but its use to diagnose common aneuploidies is not currently foreseeable from a technical point of view. At the same time, it is useful and important to start thinking about possible ways to prepare the healthcare system for the autonomy-related challenges NIPT may pose as a diagnostic test.

4.3. Expanded Targeted Use

In the future, the use of NIPT has the potential to expand to screen for a growing number of conditions such as additional and more rare chromosomal aneuploidies (other than those currently screened for), fetal CNV detection, paternity testing [56], as well as a host of more ethically contentious uses (e.g., late onset diseases or futuristic applications such as non-medical traits). The currently booming industry for genetic testing, from ancestry to direct-to-consumer 'recreational genetics' [57], attests to the fact that there is great public interest in genetic information, even if based on pure curiosity, and that weak scientific reliability is therefore no obstacle to marketing efforts [58]. Without proper regulation, future uses of NIPT that are ethically contentious, such as non-medical attributes, may end up being marketed aggressively. This may increase the pressure women and their families feel to screen for a growing number of conditions, providing them with a large amount of unreliable or difficult to interpret information that is not actionable and increases anxiety without any benefit.

Expanding the conditions NIPT screens for will further complicate pre- and post-screening counselling, and will likely lead to even more health providers forgoing informed consent altogether,

thus depriving women of choice. In addition, such expanded screening is paradoxically likely to lead to increased invasive diagnostic testing due to the low sensitivity and specificity NIPT has when screening for some of the rarer aneuploidies [59]. Moreover, it will increase the likelihood of incidental findings regarding health risks for family members, either the parents or other close relatives, who may not wish to know such risks [31]. While there are frameworks for dealing with such situations [60, 61], this outcome would still add layers of challenges and stress in the management of pregnancy.

The future expanded use of NIPT makes it critical for pregnant women to understand the purpose and potential consequences of screening, since the decision to screen can have important implications for them, their relatives, and future children. To promote reproductive autonomy, policies and guidelines must underscore the need to offer different prenatal screening choices, one of which *must* remain the explicit option to forego screening altogether, framed as a reasonable choice [16, 62]. Notably, this was recommended by the SOGC and the CCMG in their recent guideline on prenatal screening [7].

4.4. Non-Invasive Prenatal Whole-Genome Sequencing ("NIPW")

Recent papers explore the possibility of using NIPT to sequence the entire genome or exome of the fetus [63, 64], dubbed NIPW (W for "whole"). The ethical and social concerns described above regarding the expanded use of NIPT are further aggravated by NIPW since the result would be an enormous amount of information, most of which would lack certainty and clinical significance [59, 63].

The highly complex and complicated nature of the information acquired through NIPW would necessitate proper informed consent and pre- and post-test education and counselling about the interpretation of the results and the possible impact of the information, not only on the fetus, but on other family members [65]. This would prove to be a difficult logistical hurdle for most clinics offering NIPW. Furthermore, such extensive information about the genetic basis of risks to the health of the fetus has the potential to further increase patient anxiety surrounding the pregnancy, especially if the reason for undergoing screening is seen as a way to satisfy patients' "desire [for] reassurance that their fetus is healthy" [66].

Aside from autonomy concerns, routinely offering NIPW would result in "high associated costs and increase the burden on the healthcare system" [59]. From a practical standpoint, the ways in which implementing NIPW has been proposed by some authors [67] opens the door for health professionals and/or parents to set their own severity thresholds and to forego nondirective genetic counseling in some cases, thus implicitly encouraging possible eugenic practices [59, 68].

5. Conclusion

This paper began by examining the ethical and social issues associated with reproductive autonomy that are inherent in prenatal screening. It went on to present the significant benefits NIPT offers pregnant women and their families, while also explaining why, given its current implementation, NIPT poses challenges to respecting women's reproductive autonomy in the context

of prenatal screening. It then outlined some probable future uses of NIPT and the impact those could have on reproductive autonomy.

If any of the future uses of NIPT outlined in this paper materializes – and the current regulatory landscape suggests that they very well may – they will further complicate the amount, nature, and complexity of information women have access to, as well as the implications such information may have for others. This may contribute to the challenges healthcare professionals face in respecting women's reproductive autonomy. We thus suggest that the future uses of NIPT should consider respect for women's reproductive autonomy as a leading factor in responsible and appropriate implementation.

Acknowledgements

The authors would like to thank the members of the NIPT research team: Dr. Anne-Marie Laberge, Dr. Charles Dupras, Dr. Hazar Haidar, Aliya Affdal, Cynthia Henriksen, and Jessica Leclerc-Blain for fruitful discussions, as well as the peer reviewers for their extremely pertinent comments that considerably improved the manuscript. The authors would also like to thank Dr. Francois Rousseau and Dr. Sylvie Langlois for their leadership on the PEGASUS project.

Author Contributors

All authors contributed to all aspects of this study.

Funding

Vardit Ravitsky is lead-investigator and Stanislav Birko is project coordinator in a Research Project (PEGASUS) funded under the auspices of Genome Canada and the Canadian Institutes for Health Research (both non-for- profit organizations funded by the Canadian government) but that call for a small proportion of mandatory in-kind contributions from other partners. This Research Project thus receives in-kind funding from private corporations which either offer commercial NIPT tests (Ariosa Diagnostics Inc, San Jose, CA) or offer reagents and/or equipment that can be used to perform NIPT assays (Life Technologies Inc, NY, USA; Illumina, San Diego, CA, USA; QIAGEN, Hilden, GER; Perkin Elmer, Waltham, MASS, USA). This funding is at arm's-length from the scientific component of the Research Project and has no impact on the study design or its results.

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