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What is "NIPT"? Divergent characterizations of non-invasive prenatal testing strategies

Abstract:

Background: Non-invasive prenatal testing strategies that analyze fetal cell-free DNA found in maternal blood have proliferated in the past several years. Many different parties have been involved in the development, evaluation, and diffusion of NIPT resulting in rhizomatic growth of this technology. This study uses a technology studies lens to examine the ways NIPT has been constructed in informational documents, offering suggestions for future ethics analysis and policy assessment of this technology.

Methods: An inductive qualitative content analysis was conducted on 20 documents produced by vendors and health professional societies. This analysis examined the way that these groups construct the organizational aspects of NIPT, and how these ascribed structures affect what the technology is and how it interacts with the health care system. 13 vendor documents and 7 health professional society documents were analysed.

Results: An examination of vendor and health care professional society descriptions of NIPT revealed that each document describes a different version of the test, offering different claims of purpose, target population, health care professional involvement, relationship to other technologies, fallibility, and risk. We outline a spectrum of technologies that are described in documents, from wider uses of NIPT technology to very narrow uses of NIPT technology. The most common point of disagreement between narrow and wide descriptions of NIPT is when and how the test should be used.

Conclusions: The different technologies identified entail different sets of ethical questions and issues. An ethics analysis of NIPT should consider the specific features of the technology under consideration, which may open the analysis to consider more specific questions of the ethical, social, and organizational impact of that technology.

Key words: Non-invasive prenatal testing, prenatal diagnosis, prenatal screening, qualitative content analysis, technology, ethics

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Introduction:

Non-Invasive Prenatal Testing (NIPT) is a term used to refer to a strategy of prenatal testing that analyzes fetal DNA present in maternal blood. While this prenatal testing strategy is becoming increasingly available through private and public health care institutions, ethical and policy analysis is still developing (Chitty et al. 2012, Schmitz 2013, Vanstone et al. 2014). In this article, we use a science and technology studies lens to examine how NIPT is characterized as a technology by vendors and professional societies, highlighting potential challenges for ethical and policy analysis when the boundaries of NIPT technology are not contextualized in a clear and specific way. We accomplish this by conducting a qualitative content analysis of information documents, using the guiding question: "How is the technology of NIPT constructed in informational material produced by vendors and professional societies of health care providers?"

What is NIPT? Most producers, users, and researchers of NIPT would likely agree that it is a way to gain information about fetal genotype by examining samples of fetal DNA obtained from the mother's blood. The same parties may disagree on whether or not it should be administered by a clinician or available directly from vendors, what type of genetic material is analyzed, the method of analysis, reliability of analysis, target population, time of use in the antenatal care pathway, purpose of obtaining this information, and the requirement for other technologies before, during, and after the use of NIPT. These diverse characterizations of NIPT may reflect the atypically quick

evolution of NIPT (Bianchi et al. 2014) at the hands of its promoting stakeholders (multiple vendors, business development proposals, certain clinicians, some professional organizations). The rapid diffusion of NIPT has been driven by vendors keen to capitalize on parents' desire for a non-invasive test that will help them to avoid having a child with certain characteristics such as a particular sex, inherited trait, or trisomy condition (Yi et al. 2013, Lewis et al. 2014, LLC 2014, Hill, Fisher, et al. 2012). As a result of the involvement of many different stakeholders, NIPT has grown in many directions, been proposed for a variety of uses, been linked to a number of different technologies, and targeted at multiple patient populations. This rhizome-like growth is not always explicitly recognized in the scientific and clinical literature, where many authors treat their conception of NIPT as the only way of using this technology.

Characterizing NIPT as a clearly defined, monolithic technology not only disguises much of the tension and confusion about what technology "NIPT" refers to, but also obfuscates current and potential uses of this technology from ethical and ultimately policy consideration. Understanding the context in which a technology will be used is an important foundation for ethical analysis. This focus on the contextualized use of a technology subscribes to the view that ethical implications are not embedded within the apparatus of the technology, but within the context and application of that technology (Lehoux 2006, Lehoux and Blume 2000, May 2006, Heitman 1998). With NIPT, this means that the ethical issues are not related to the particular genetic assay techniques used to analyze the fetal DNA, but to the construction of a need for knowledge about the fetal genotype and related constructions of the risks acceptable in

gaining that knowledge, the claims made about the accuracy of that analysis, the groups who are given (or restricted from) accessing that analysis, the conditions that are tested for, the way those conditions are chosen for inclusion in the test, etc. The use of NIPT may be ethically different depending on when it is offered, how the test fits within the antenatal care pathway, and what counselling is included with the offer (Sayres, Allyse, and Cho 2012, Deans and Newson 2012).

Ethicists are often interested in examining the unintended, unexpected, or inevitable "side effects" of a technology, that is, the effects that a technology has outside of its intended purposes (Giacomini, Winsor, and Abelson 2013). Without understanding the particular contextual details of how NIPT is used in a particular setting, ethical consideration of these types of "side effects" is challenging. This contextual information is needed to understand how NIPT is changing reproductive care and decision-making and the potential impacts for women, clinicians, and people with disabilities. Examining the ways in which NIPT is implemented may open up new avenues of ethical inquiry related to its place in the clinical pathway, the role and actions of health professionals, the impact on patients lives, the re-shaping of antenatal care practices, and the normative values espoused by the offer of the technology itself (Schmitz 2013, Giacomini, Winsor, and Abelson 2013, Heath, Luff, and Svensson 2003). This may assist in broadening ethical consideration of NIPT beyond the common issues of reproductive autonomy, informed choice, and impact on people with disabilities - important considerations, but only part of the potential impact of this new technology (Schmitz 2013).

Methodology and methods

This study is informed by the theoretical framework known as social shaping of technology (Wajcman 2010, Clausen and Yoshinaka 2004, Russell and Williams 2002, Williams and Edge 1996). This is a constructivist framework that conceptualizes society and technology as mutually constitutive; shaping each other through socially negotiated features and meanings (constructs) (Clausen and Yoshinaka 2004, Russell and Williams 2002, Williams and Edge 1996). We were specifically interested in how vendors and professional societies construct the organizational aspects of NIPT, and how these ascribed structures affect what essentially the technology is and what it can do. In turn, the availability or promotion of particular configurations of the technology create new opportunities and imperatives for its use, and affect societal views of normalcy, health, etc (Tremain 2005, Vanstone, Kinsella, and Nisker In Press, Parens and Asch 2000, Rapp 1999).

To investigate how NIPT is constructed and promoted, we conducted an inductive qualitative content analysis of prescriptive documents authored by vendors and professional societies. Professional societies and test manufacturers write and distribute these documents to introduce NIPT's potential users to what the technology "is" and advise them on why, when, and how to use it. These carefully articulated visions provide a unique source for understanding key stakeholders' "organizational versions of reality" of NIPT (Atkinson and Coffey 2010). Documents both reflect the views of their authors and influence the views of their audiences (Atkinson and Coffey

2010, Miller and Alvarado 2005, Prior 2003) and in doing so participate actively in shaping NIPT practices and the technology's role in health and health care.

The guiding question of this study is "How is NIPT constructed in informational material produced by manufacturers and professional societies of health care providers?" We qualitatively analyzed the content of these documents for how NIPT is described to its users, what claims are made about the purpose, capabilities, and audience of this technology. We also analyzed arguments supporting key claims.

Data collection

Following constructivist interpretive methodology, we approached NIPT informational materials as social interactions between key authors (professional societies, manufacturers) and audiences (providers, patients). We analyzed the various ways each interaction constructs NIPT, with particular attention to the role of authors' assumptions about target audiences and their interests (Garfinkel 1967, Hodder 2003). These two primary sources of education about NIPT – professional statements, education materials – often serve as authoritative bases for further constructs to be found in, e.g., media coverage, individuals' opinions, etc. In this study, we focus on the primary "authoritative" materials.

Professional societies typically publish their statements in peer-reviewed journals or other peer venues, and expect readers to be providers or other health system professionals. Health care professionals have reported nearly unanimous reliance on these guidelines when offering NIPT (Sayres et al. 2011). Manufacturers publish their educational materials publicly, but tailor and direct providers vs. lay readers to different

versions. These differentially crafted documents reflect important assumptions about who the different readers are, and the distinctive knowledge, experience and values they bring to interpreting the content (Atkinson and Coffey 2010).

We systematically collected all current (as of January 31, 2014) versions of English-language documents in each category: professional statements, manufacturer information for providers, and manufacturer information for lay people. Manufacturers' materials were downloaded from their websites. NIPT is marketed by seven companies, Sequenom (MaterniT21 test), Ariosa (Harmony test), Illumina (Verifi test), BGI (Nifty test), Lifecodexx (Praenatest test), Berry Genomics (BamniTest) and Natera (Panorama test). If a company offered an information brochure or pamphlet on their website, we used that source, if not, we used the relevant web pages. The sections on web pages that were selected directed information about the test at pregnant women and/or health care providers. We successfully collected educational materials for both audiences from 6 companies. Berry Genomics only provides one source of information which we categorized as provider, given the level of scientific detail provided. We analyzed 6 documents for laypeople and 7 for providers (Table 1).

We collected professional society statements from Europe, Australia, New Zealand, Canada, and the United States through searches of guideline databases (National Guideline Clearinghouse, Canadian Medical Association Infobase, Guideline International Network) and by searching the websites of the relevant member organizations of FIGO (Federation of International Gynecology and Obstetrics). We used search terms including "non-invasive prenatal diagnosis", "non-invasive prenatal

test", "non-invasive prenatal screening", "cell-free fetal DNA". Statements were included if they were publicly available, most current versions, addressed non-invasive prenatal testing, were written in English, included recommendations for clinical practice, and were produced by an association of health care providers. We retrieved 7 eligible professional statements, although one mentions NIPT only very briefly (Royal Australian and New Zealand College of Obstetricians and Gynecologists 2013). Professional society statements are shown in Table 1(Chitty and Crolla 2009, Royal Australian and New Zealand College of Obstetricians and Gynecologists 2013, American College of Obstetricians and Gynecologists 2012, Benn et al. 2013, Devers et al. 2013, Gregg 2013, Langlois and Brock 2013) .

Analysis

All documents were coded following conventions of constructivist grounded theory (Charmaz 2006) and analysis followed the typical phases of qualitative content analysis: immersion, reduction, and interpretation (Forman and Damschroder 2008, Atkinson and Coffey 2010, Miles, Huberman, and Saldaña 2013). Analysis began with an open-coding stage involving close reading and line-by-line coding followed increasingly focused coding and re-coding stages; two researchers conducted the coding. Each coding stage iterated with full team review and discussion of coding reports, emerging categories and findings. Coding was guided in part by sensitizing concepts intended to capture key organizational features of diagnostic technologies, i.e.: envisioned users, purposes of testing, and NIPT's relationship to other technologies (e.g., other diagnostics, or therapeutic interventions). Constant comparative analysis

was used to analyze similarities and differences between authors, intended audiences, categories of information, support for claims, and also to identify potential content absent from some documents. N-Vivo® 10 (QSR International) software was used to manage the data.

As all of our data are publicly available, research ethics approval for this study was not necessary.

Results

Each document we reviewed described a particular version of NIPT. There are significant discrepancies and some direct contradictions across the different document's descriptions of NIPT as well as several similarities. NIPT is described with many types of information, such as the purpose, relationship to other technologies, target population, recommendations for counselling, accuracy and fallibility. Each document source portrays NIPT along these and other categories, constructing a distinct version of the technology. Looking at the different versions of NIPT across sources, a variety of related but different technologies is identified. Some of these versions describe a wider variety of uses for NIPT, and some describe a much narrower range of uses. These descriptions fall along a spectrum, with different documents calling upon a variety of wider and narrower uses depending on the category of information being used. On one end of the spectrum, "Narrow" descriptions of NIPT proscribe a very constrained way of using this technology, with clearly defined target population, purpose, and relationship to existing prenatal testing technologies. On the other end of the spectrum, "Wide" uses of NIPT are vaguer about how the technology might be used, encompassing a greater

number or variety of potential uses. The versions of NIPT identified in each particular source documents do not fall into either end of the spectrum, but exist somewhere along the continuum. Table 2 summarizes the different ways in which wide and narrow uses of NIPT are constructed.

Characterizations of "narrow" uses of NIPT

Narrow uses for NIPT were most commonly found in documents produced by professional societies, and in a small number of vendor pamphlets that made explicit reference to professional society documents (e.g. Praenatest). Many statements encouraging a narrow use of NIPT were justified by reference to what evidence was available for that use. In some instances, a wider use of the technology was discouraged by these professional society documents because of a lack of evidence.

Narrow use stereotype

NIPT is a screening test of uncertain accuracy. It should only be used by women with singleton pregnancies who are at increased risk for a limited number of conditions. "Increased risk" is determined by the physician or a genetic counsellor and may take into consideration factors such as test results from earlier screening tests, maternal age, or previous trisomy pregnancies. The main purpose of using NIPT is to decide whether or not to proceed with invasive diagnostic testing. A negative result after NIPT may make a woman feel more comfortable choosing not to engage in invasive diagnostic testing. A positive result from NIPT should be confirmed with invasive testing. Significant counselling is required both before and after NIPT. A genetic counselor should be involved if a positive result is received.

Purpose

Documents espousing a narrow use of NIPT are clear that the purpose of the test is to screen for various conditions to provide information to assist in the decision of whether or not to pursue invasive diagnostic testing. This stance is typical in professional society documents, but uncommon amongst patient brochures, with one exception: "help women and their providers decide whether to have an invasive diagnostic procedure" (Illumina 2014a).

Relationship to other technologies

In the "narrow" characterization of NIPT, there is a clear relationship between NIPT other prenatal screening and diagnostic tests. Many documents describe a positive result from initial prenatal screening tests as one possible impetus for NIPT testing, (BGI Health 2014a, Illumina 2014b, Lifecodexx 2013a, b, Natera Inc. 2014). Some documents are explicit that positive results from NIPT should be confirmed with further invasive testing, (Illumina 2014b, Lifecodexx 2013a, b) especially the professional society statements, most of which emphatically state that confirmatory invasive testing is required (American College of Obstetricians and Gynecologists 2012, Gregg 2013, Benn et al. 2013, Devers et al. 2013, Langlois and Brock 2013).

Screening or diagnosis

Professional society documents are explicit that there is not sufficient evidence to support the use of NIPT as a diagnostic test and so it should be considered a screening test only, with confirmation via invasive diagnostic testing if desired. (American College of Obstetricians and Gynecologists 2012, Gregg 2013, Benn et al. 2013, Devers et al.

2012, Langlois and Brock 2013) This is not echoed by most vendor documents, with only a few explicitly stating that NIPT is a screening test (Illumina 2014b), although others imply it by stating that their test "assesses the risks" of trisomy (Ariosa Diagnostics 2013a, b) or by comparing their test to other screening tests (Natera Inc. 2014).

Target Population

A narrower use of NIPT states that it is only useful in women who are known to have increased risk for fetal aneuploidy , potentially by reason of advanced maternal age, prior positive screening results, or previous aneuploid pregnancies (BGI Health 2014a, b, Illumina 2014a, Lifecodexx 2013a, Natera Inc. 2013, Sequenom 2013b, American College of Obstetricians and Gynecologists 2012, Benn et al. 2013, Devers et al. 2013, Langlois and Brock 2013). Several professional society documents are clear that this test "should not be offered to low-risk women or women with multiple gestations because it has not been sufficiently evaluated in these groups" (American College of Obstetricians and Gynecologists 2012). A narrow use of NIPT limits it to singleton pregnancies (American College of Obstetricians and Gynecologists 2012, Benn et al. 2013, Lifecodexx 2013b).

Fallibility

There were many limitations of the test mentioned by professional society documents, including lists of conditions NIPT does not detect (American College of Obstetricians and Gynecologists 2012, Devers et al. 2013, Gregg 2013), some of which are detected by traditional screening or invasive testing (Gregg 2013, Langlois and

Brock 2013); lack of evidence of efficacy in particular populations (American College of Obstetricians and Gynecologists 2012, Benn et al. 2013, Devers et al. 2013, Langlois and Brock 2013, Chitty and Crolla 2009); fallibility of existing validation studies (Benn et al. 2013, Chitty and Crolla 2009); sensitivity and specificity rates are not equal across all trisomy conditions (Gregg 2013); issues with independent laboratory standards and quality control (Benn et al. 2013, Langlois and Brock 2013); longer time to receive results from NIPT than invasive diagnostic testing (Gregg 2013); false negative and positive rates (American College of Obstetricians and Gynecologists 2012, Gregg 2013, Benn et al. 2013, Devers et al. 2013, Langlois and Brock 2013); the possibility of the need to re-draw blood and re-test if the percentage of fetal DNA retrieved is low, more likely in women of higher BMI and those in earlier stages of pregnancy (American College of Obstetricians and Gynecologists 2012, Gregg 2013, Benn et al. 2013, Langlois and Brock 2013); variability in accuracy between brands of NIPT due to the use of proprietary bioinformatics, the performance of which requires more evaluation to determine which is most effective (Gregg 2013, Benn et al. 2013). Some of these limitations are mentioned in the vendor documents for providers, especially false negative and false positive rates (BGI Health 2014b, Illumina 2014b, Lifecodexx 2013b, Natera Inc. 2014, Sequenom 2013b) and the conditions not tested for (Illumina 2014b, Lifecodexx 2013b, Natera Inc. 2014, Sequenom 2013b). The potential for re-test is mentioned by Panorama (Natera Inc. 2014) and Praenatest (Lifecodexx 2013a).

Characterizations of "wide" uses of NIPT

Wider uses are characterized in two ways: through explicit statements about wide use and through ambiguous, vague, or obfuscating statements that allude to wider potential usages. For instance, if the target population is not discussed in a vendor pamphlet, some readers may understand the target population to be all pregnant women. Wider uses for NIPT were most commonly found in vendor pamphlets.

Wide use stereotype

NIPT is a simple and very accurate test that can be used early in pregnancy by any pregnant woman to reliably identify the presence or absence of a large number of trisomy and sex-chromosome conditions. This test overcomes the weaknesses of existing prenatal tests by offering very accurate information with no physical risk to the fetus. The purpose of this test is to make available information that will provide reassurance, relief, and additional "options" to women. This test will also allow women to avoid the physical risk of miscarriage or infection associated with invasive testing such as amniocentesis. This test is facilitated by physicians, who should provide information on the benefits and limitations of this test to help a woman identify whether or not she wishes to take this test.

Purpose

A wide use for NIPT is characterized by very vague statements about the purpose of NIPT with positive phrases such as "peace of mind" (Panorama Pt), "reduce fear" (Praenatest patient), or "knowledge is empowering" (Sequenom 2013a). These platitudes were also present in some vendor documents for providers. For example, MaterniT21 tells providers that "Expectant couples are often overwhelmed with

information. They're anxious. They're worried. And they're looking to you for answers"(Sequenom 2013b). Professional society documents were not as likely to address the issue of worry or anxiety, although the ISPD position statement did state that "all approaches to risk assessment appear to provide an opportunity to re-assure most women that their fetus is unlikely to be affected by a chromosomal disorder"(Benn et al. 2013).

All documents mention that the purpose of NIPT is to provide information about the presence of particular conditions, giving at least some information about the conditions included in the test. However, the amount and detail of the information about conditions varies significantly, from brief mentions that it tests for "certain genetic conditions such as Down syndrome, Edwards syndrome and Patau syndrome" (Natera Inc. 2013) to more detailed descriptions of what a chromosome is and what Trisomy 21, 18, and 13 are like: "children with Down syndrome have delays in both intelligence and development. Babies with Down syndrome also have higher chances for health problems" (Sequenom 2013a).

The documents rarely address the issue of *why* a woman might want information about the likelihood of a trisomy condition or sex chromosome abnormality, or what options are available in the event of a positive result. In patient brochures, this information is conspicuously absent, sometimes obviated by comments addressing what might happen in the event of a negative finding. For example, the PraenaTest patient brochure says that a negative NIPT test will " help reduce fears and ensure an undisturbed course of pregnancy" (Lifecodexx 2013a). In provider brochures, we see

language such as "giving the patient and physician ample time to make a fully educated position on how to proceed" (BGI Health 2014b) or "make well informed decisions" (Sequenom 2013b) rather than details about what options are available.

Relationship to other technologies

NIPT is most frequently compared to prenatal screening tests (e.g., integrated prenatal screening, maternal serum screening) and invasive diagnostic tests (e.g., amniocentesis, chorionic villus sampling). Documents espousing a "wide" use of NIPT tend to emphasize it as a substitute for other prenatal tests, either explicitly, by stating that NIPT can help avoid invasive testing (BGI Health 2014a) or implicitly, by favouring NIPT in a direct comparison. For example, the Harmony patient document states that "other screening tests such as serum blood tests and ultrasound are also non-invasive, but have false positive rates of up to 5% and miss detection of up to 30% of fetal trisomy 21 cases. ... Diagnostic tests such as amniocentesis or chorionic villus sampling (CVS) are accurate for detecting fetal trisomies, but they are invasive and pose a risk for fetal loss" (Ariosa Diagnostics 2013a). This brochure does not explicitly state that Harmony is a replacement for these tests, but neither does it state or imply that Harmony should be used in conjunction with any other test.

Screening or diagnosis?

There is significant tension around the issue of whether NIPT results are accurate enough to be diagnostic or if it should be considered a screening test. Many vendor documents (for both patients and providers) skirt the screening/diagnosis issue by using words such as "detect", "test", "evaluate" or "assess" therefore avoiding having

to declare whether their test is for screening or diagnosis (Ariosa Diagnostics 2013a, b, BGI Health 2014a, b). These vendor pamphlets sometimes describe the role of further invasive testing "for elaboration" rather than confirmation of NIPT results. For example, the Praenatest patient brochure states that "further examination is necessary to diagnose a genetic reason for the trisomy"(Lifecodexx 2013a). MaterniT21 and Panorama sidestep the issue of whether their test is intended for screening or diagnosis, avoiding language that implies either purpose and not mentioning the need for additional testing to confirm diagnosis (Sequenom 2013a, b, Natera Inc. 2013). Berry Genomics states that their test is "being increasingly requested as the primary prenatal diagnostic test" (Berry Genomics 2013).

Target population

The documents communicate different target populations for NIPT. The widest use of NIPT describes the target population as any pregnant woman (Ariosa Diagnostics 2013a, b), including those with twin or multiple gestations (Ariosa Diagnostics 2013a, Illumina 2014a, Sequenom 2013b). Some documents specify other populations who may be interested in NIPT, including women who conceived via IVF or who have used egg donors (BGI Health 2014b, Ariosa Diagnostics 2013b, Sequenom 2013b, Illumina 2014b).

Fallibility

In comparison to documents from professional societies, those from vendors targeting patients identified the fewest number of limitations or ways that NIPT is fallible, often mentioning only that "no test is perfect"(BGI Health 2014a) and suggesting that

women ask their doctor about limitations(Sequenom 2013a). When surrounded with statements about "clear, powerful results"(Sequenom 2013a), this de-emphasizes the limitations of the test. Other common statements about fallibility include mention of what is not tested for (e.g., mosaicism, partial trisomies, translocations) (Ariosa Diagnostics 2013a) or a statement about negative results not ensuring an unaffected pregnancy (Illumina 2014a, Sequenom 2013a). Mentions of false positive rates and false negative rates were often minimized with language such as "false positive and false negative results may occur in rare cases" (Sequenom 2013a) or "of the 95,000 NIFTY tests performed so far, there have been zero cases of false-negative results and a false-positive rate of five one-thousandths of one percent (0.005%)"(BGI Health 2014a), which while mentioning the possibility of false-positive and false negative rates, minimizes this possibility.

Discussion

In our analysis of vendor and professional society documents, we identified a disjuncture between vendor and professional society claims about NIPT. Each document described NIPT in a slightly different way, constructing their own version of the technology that varied according to purpose, target population, fallibility, relationship to other technologies, etc. The most common area of disagreement between the two groups is when and how NIPT should be used, with potential uses varying widely from first-tier screening for all pregnant women to second-tier screening for only women known to be at high risk of particular trisomy conditions.

Given the variety of ways NIPT is characterized in the documents we reviewed, we suggest that it can be considered to be multiple technologies employing similar strategies of analyzing fetal DNA via maternal blood. A technology is not just the physical apparatus or laboratory analysis technique but the wider way that these tools are employed, including the way that they are organizationally constructed with a particular purpose, target population, and resulting effects on users (Oudshoorn, Pinch, and Pinch 2005, Bijker et al. 2012).

Published ethical analyses so far reflect this dissonance in the definition and use of NIPT and handle this issue in different ways: considering potential uses of NIPT not yet clinically available (de Jong et al. 2009), acknowledging the uncertainty of the technology and relying on assumptions (e.g. of accuracy) to characterize NIPT for the purpose of ethical analysis (Benn and Chapman 2009), choosing a particular vendor's version of NIPT to critique (Kaposy 2013), identifying the relationship between ethical consequences and the point in the antenatal pathway in which NIPT is used, (Schmitz 2013, Schmitz, Netzer, and Henn 2009, Deans and Newson 2012) and acknowledging the likelihood of technology expansion while highlighting potential issues of many different types of use, without defining a particular use (Allyse et al. 2013).

As a result of the variety of ways NIPT is described, it is difficult to contextualize this technology for ethical analysis. Contextualization of a technology is a constructive activity, with the analyst constructing and negotiating the boundaries, divisions, and trade-offs between technologies (Giacomini 1999). Whether or not the act of contextualizing a technology is acknowledged, it takes place through activities such as

delineating the scope of the disease or problem the technology aims to address; defining relevant management, economic and implementation issues; defining relevant patient populations, etc (Levin et al. 2007, Lehoux and Blume 2000, Giacomini 1999) . This contextualization work provides the foundation for future assessment or evaluation of the technology, and therefore shapes the outcomes of that endeavour (Giacomini 1999).

Contextualizing a technology before evaluating or analyzing it is important because it enables the analyst to examine how that technology will operate as part of a larger technological system, therefore opening the possibility of considering the impact that technology may have on all the other elements in that system as it interacts, substitutes, complements or conflicts with other components of the system (Hughes 2012).The effect NIPT will have on the prenatal care system will depend on when, how, and with what supports it is introduced. Analyzing the ethical implications of NIPT without considering these specific contextual issues tends to result in the ethical analysis of abstract concepts (e.g., reproductive autonomy, informed choice) to the exclusion of specific issues (e.g., availability of care for people in rural and remote locations) ((Silcock et al. 2014, Sayres, Allyse, and Cho 2012, Schmitz 2013). *Both* abstract and specific issues are important to include in an ethical analysis of a health technology. Future ethical analysis of NIPT may wish to examine the impacts of specific versions of this technology, such as the involvement of industry and activist stakeholders, implications of an expanded range of conditions, availability of care for people in rural and remote areas, and change in patient-provider and generalist-

specialist interactions (Silcock et al. 2014, Sayres, Allyse, and Cho 2012, Schmitz 2013).

The pace of change witnessed so far in the development of NIPT (Bianchi et al. 2014) and the lack of regulation and consensus standards make a single authoritative definition of NIPT less and less likely, requiring those who wish to study the technology (e.g., for ethical analysis or health technology assessment) to articulate the version of the technology they wish to consider. While the ambiguity in definitions of NIPT requires extra thought and contextualization, this ambiguity about how NIPT could or should be used also creates an opportunity for ethical analysis to inform policy and regulation. At this point in time, potential uses of NIPT are still being constructed, and there is room for flexibility before this technology becomes stabilized in a narrower range of uses (Pinch and Bijker 1984, 1987). Ethicists working in this area may find it useful to clearly articulate the version of NIPT they are considering, for instance, by making note of any assumptions they are making about the technology (Benn and Chapman 2009), or considering how ethical issues may change with different deployments of the technology (Deans and Newson 2012).

Limitations

This paper considered the versions of NIPT as constructed by two types of organizations which claim authority to create a version of this technology: vendors and health care provider organizations. Future research may wish to examine how other groups construct NIPT, potentially shedding light on which versions of the technology have gained traction in different circles, or become picked up in popular usage.

While this paper examines the way that NIPT is currently constructed by vendors and professional societies, it is important to appreciate that technologies change over time and NIPT seems likely to change more quickly than most, given the number of new applications currently in development (Hill, Barrett, et al. 2012, Li et al. 2007, Saito et al. 2000, Gonzalez-Gonzalez et al. 2002, Nasis et al. 2004, Saker et al. 2006). Two teams have now sequenced an entire human genome from fetal cells. Soon, any genetic condition or trait could be suggested by NIPT (Fan et al. 2012, Hui and Bianchi 2013).

Conclusion

In this paper we have argued that NIPT is not one technology, but several technologies which use a similar analytic process to provide information about fetal DNA. These technologies differ in terms of proposed purpose, relationship to other technologies, target population, and conditions tested for. The various conceptions of NIPT entail different ethical implications. We encourage those conducting ethical analyses of NIPT to be specific and particular about what kind of NIPT they are considering. This may mean detailing the related patient population, offer, counselling, purpose, conditions tested for, etc. when analyzing ethical issues related to NIPT.

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