HHS Public Access

Author manuscript

Hastings Cent Rep. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Hastings Cent Rep. 2017 March ; 47(2): 41–49. doi:10.1002/hast.690.

Towards an ethically sensitive implementation of non invasive prenatal screening in the global context

Jessica Mozersky, PhD,
Assistant Professor, Washington University School of Medicine, 4523 Clayton Ave., CB 8005, St. Louis, MO 63110

Vardit Ravitsky, PhD,
Université de Montréal, Québec

Rayna Rapp, PhD,
New York University

Marsha Michie, PhD,
University of California, San Francisco

Subhashini Chandrasekharan, PhD, and
Duke University

Megan Allyse, PhD
Mayo Clinic

Abstract

Cell-free DNA (cfDNA) screening is an emerging prenatal technology available in 90 countries. Despite its rapid global diffusion, there is a gap in knowledge about its implementation outside of North America and Europe including low to middle income countries. To address this, we organized an international comparative workshop to explore the ethical and social implications of the global expansion of cfDNA screening. We describe 8 key insights that arose from discussions to illustrate how bioethical discussions and normative frameworks that originate and reflect North American and European ethical priorities can be enriched by attending to the importance of local context. The utility and ethical implications of cfDNA screening are highly variable and dependent upon local healthcare systems, cultural, economic, and socio-political contexts and needs. We call for a more subtle, dynamic and contextual understanding of the international spread of cfDNA screening, which will evoke diverse challenges across different contexts.

Keywords

ethics; non invasive prenatal genetic testing; global expansion cultural context

Non-invasive prenatal screening using cell-free DNA (cfDNA screening) has been hailed by some as a potential ‘paradigm shift’ in prenatal genetic screening.[1] cfDNA screening

Corresponding Author: Jessica Mozersky, PhD, Assistant Professor, Washington University School of Medicine, 4523 Clayton Ave., CB 8005, St. Louis, MO 63110, Phone: 314-454-8638, jmozersky@wustl.edu.

analyzes cell-free placental DNA circulating in maternal blood to provide information about certain fetal chromosomal disorders, such as Down syndrome, early in pregnancy and without risk to the fetus. The diagnostic standard, amniocentesis or chorionic villus sampling, poses a small but real risk of procedure-related miscarriage (greater in low-resource settings), which many women find unacceptable. cfDNA screening represents an improvement over previous prenatal serum screening methods in sensitivity and specificity, potentially reducing the number of pregnancies that require diagnostic confirmation due to false positives.[2] Since cfDNA screening can be conducted on a maternal blood draw, testing can be done remotely, potentially providing accurate screening information in resource-poor areas with reduced access to skilled sonographers or prenatal diagnostic practitioners. Nevertheless, it is a screening test and high-risk results require diagnostic testing for confirmation, which in turn necessitates skilled practitioners.

Two unique aspects of cfDNA screening distinguish it from commonly used prenatal tests: its provision almost exclusively by commercial companies and its rapid global expansion since its introduction in late 2011. The intellectual property underlying cfDNA screening technology is primarily held by six for-profit companies (4 US-based and 2 based in China). However, a growing number of companies are developing tests for regional and national markets in low and middle income countries, and many are seeking patent protection. Although the exact numbers are proprietary, cfDNA screening companies reported at least 800,000 tests performed worldwide by 2014.[3, 4] As of 2015, cfDNA screening was available in over 90 countries, demonstrating the increasingly globalized nature of genomic technologies.[5] The commercial provision of cfDNA screening also contributes to a rapid expansion of the tests included in cfDNA screening panels (including sex chromosome anomalies, rare sub-chromosomal microdeletions and aneuploidies, and most recently the entire fetal genome); often in advance of peer-reviewed validation studies and with poor data on clinical utility.[6] In a competitive commercial environment, the rationale for adding more conditions is presumably to carve out bigger market share or differentiate market segments, using the claim that more information is always better for the consumer.[7] Thus commercialization and rapid global expansion are intertwined, with the promise of increasing market share driving the rapid global spread of cfDNA testing.

The benefits of cfDNA screening are generally framed - by both providers and commercial laboratories - as enhancing reproductive autonomy and choice by providing an earlier, simpler, and more accurate screening, while potentially reducing the need for invasive follow up testing.[6] Some studies have found that women report experiencing several of these benefits.[8, 9] Nevertheless, the ethical drawbacks of cfDNA screening are linked to the same characteristics: the simplicity of cfDNA screening may compromise informed consent, especially if it becomes routinized and indistinguishable from the many blood tests women already undergo during pregnancy. Additional ethical concerns surround abortion and disability rights; justice and inequitable access to testing; and increasing false positive rates (often due to incidental findings about the mother) as more conditions are added.[5,6] The majority of the literature has explored these issues empirically or conceptually from a European or North American vantage point, one that assumes normative priorities such as individual reproductive autonomy and the clinical availability of maternal health care or prenatal screening programs within which cfDNA screening is offered. While its

implementation has raised both challenges and opportunities, very little is known about "real world" experiences and the implications of the rapid introduction of cfDNA screening outside of North America and Europe, especially in low and middle income countries (LMIC).[10, 11, 12, 13]

To begin addressing this gap in knowledge, we organized an international, 4-day, comparative workshop to explore the ethical, legal, social, economic, clinical, and practical implications of the global expansion of cfDNA screening.[14] The workshop was hosted by the Brocher Foundation in Geneva, with support from the Wellcome Trust. It included 24 participants, representing perspectives from Argentina, Australia, Canada, Chile, China, Hong Kong, India, Israel, Japan, Lebanon, Nigeria, Singapore, South Africa, Switzerland, the United Kingdom (UK) and the United States (US). The participants were invited on the basis of their publicly presented or published work on the implementation of cfDNA screening, including in resource-poor contexts, and consisted of clinicians, laboratory scientists, genetic counselors, bioethicists, and social scientists. Participants represented a diverse array of health care systems, legal frameworks, economic, cultural and religious contexts that helped foster comparisons between and within regions. Participants delivered presentations on the status and use of cfDNA testing locally, followed by group discussions. Breakout sessions were organized around particular themes identified by the organizers during the workshop such as globalization, motherhood/gender, disability, and resource allocation. While the workshop was not globally representative, especially of the most impoverished countries, it was the first of its kind and provides a starting point for investigating the effects of the global expansion of cfDNA screening.

The meeting highlighted the ways in which "Western" normative assumptions permeate ethical and clinical discussions surrounding cfDNA screening and the genetic conditions for which it is offered, underlining the need to take into account global and intra-national variation.[1] Normative frameworks are essential for guiding the ethical implementation of cfDNA screening, yet bioethical concepts such as "personal reproductive autonomy" and "procreative freedom" may also have a homogenizing effect that diverts attention away from local contexts and cultures. Because some cultural contexts employ a more relational understanding of autonomy than others, an ethical implementation of cfDNA screening would entail different conceptions of autonomy and consent.[15] Moreover, the diversity of contexts will not necessarily map neatly onto geographic or national borders, further emphasizing the challenges of cfDNA screening as it expands globally.

In this article, we describe 8 key insights that arose from 4 days of workshop discussions. We use these insights to illustrate how bioethical discussions can be further enriched by drawing attention to the importance of local context when thinking about the global expansion of new genomic technologies. We quickly discovered that many of the ethical concerns regarding cfDNA screening are present everywhere, including North America and Europe, albeit in different guises and with varying effects. As a result, we toggle back and forth between different national contexts represented during the workshop in order to

[1]This includes the language used and we agreed to use LMIC rather than developed/developing or First and Third World, and avoided the term "non-Western."

emphasize the complex and subtle ways that cfDNA screening will evoke diverse challenges across different contexts. We specifically include examples from the US to highlight how binary modes of thinking that delineate "Western" and "non-Western" ethical concerns may fail to capture our many shared, as well as nationally-specific, challenges.

By taking an ideographic and relational approach we aim to bring "practice into theory…to inform theoretical concepts with a more situated and contextualized interpretation" rather than a top down application of normative ethical theory to guide policy and other decisions.[16] This approach is an especially useful conceptual and analytical tool for our analysis of the global spread of cfDNA screening as it "rejects the notion that an individual can be abstracted from social being and ecological place."[16] We call for a more subtle, dynamic and contextual understanding of the international spread of cfDNA screening, which belies a one-size-fits-all view of policy.

Women's Health and Gender in Context

Patient Decision Making: the limits of autonomy

The construction of informed consent that dominates much of the bioethics literature–of an act undertaken by an autonomous individual making informed, rational decisions–does not reflect the lived reality of prenatal screening decision-making in many cultural contexts.[15] In India, for example, prenatal testing decisions are often familial, involving extended family members and in-laws. In some instances, husbands, fathers, or other male relatives make these decisions. Moreover, in contrast to the kind of non-directive counselling advocated throughout North America and Europe, in countries such as India, Nigeria or Lebanon, patients look to clinicians to make concrete recommendations about clinical decisions.

The view of cfDNA screening as enhancing individual autonomy and reproductive rights may mask the ways in which its availability may not advance "individual choice" and could exacerbate pre-existing pressures women experience from family - and healthcare providers - to make certain reproductive decisions. The influence of families and communities on the reproductive decisions of individuals may be deeply woven into individual choices even if decisions are made "autonomously" and without involving others.

The "extreme individualism" that can be conveyed by ideas of individual freedom and rights runs the risk of "non-recognition and rejection" of differences among women, especially in the global context.[17] While not repudiating the concept of autonomy or the value of individuality, a relational and feminist approach to autonomy must acknowledge that "persons are socially embedded…formed within the context of social relationships and shaped by a complex of intersecting social determinants such as race, class, gender and ethnicity.[15] Importantly, this conception does not negate the necessity of *informed* consent but redirects our attention to the familial and relational, rather than individual, nature of decision making in many contexts. It is crucial to consider that decisions are not necessarily made by individual women, but in relation to others, in order to appropriately implement cfDNA screening in a culturally-sensitive manner that takes into account local norms and needs.[15, 16, 18]

Abortion

In many countries, including much of Latin America and Africa, abortion is illegal or severely restricted. In these locales, terminations may be practiced clandestinely and at great risk to women's lives and reproductive health. Although termination of "affected" fetuses is not the stated goal of cfDNA screening (or any form of prenatal screening) - women may use screening and testing for information, reassurance, or to prepare for the birth of their child - implementing cfDNA screening in countries that do not provide safe and legal access to abortion raises particular ethical concerns.[19] In the context of restricted access to safe abortion, cfDNA screening may exacerbate the significant potential harms to which women are subjected if they wish to end a pregnancy following confirmation of their cfDNA screening results. Women may be pushed to use illegal means and/or suffer psychological or physical consequences from lack of access to safe termination. Even where abortion is entirely prohibited, the vulnerabilities women experience are complex and diverse; women with resources are far more likely to be able to access safer abortions than those living in poverty.[20]

The steadily decreasing availability of abortion in the United States illustrates how women may face similar circumstances in very different sociopolitical contexts. Recent US federal and state legal restrictions now include gestational limits and criminalization of second trimester abortions, mandatory waiting periods of up to 72 hours and ultrasound requirements prior to abortion (including in instances of rape and incest), bans on non-surgical abortions, and highly restrictive physician and hospital requirements that effectively force many abortion clinics to close because they do not meet certain requirements like hospital admitting privileges.[21] In some states, there may be only one abortion provider, effectively making it impossible for some women, especially women of lower socioeconomic status, to access safe abortion.[21] While cfDNA screening is rapidly expanding in the US, and is increasingly covered by private and state-based insurance plans, women, particularly women in rural areas may nonetheless lack access to abortion services, placing a severe restriction on their reproductive choices following cfDNA screening.[22] This illustrates the limitations of defining ethical issues along geopolitical boundaries, which can have a similarly homogenizing effect as the concept of "autonomy", in failing to recognize how particular contexts and socio-political circumstances can *make* or *render* some women, regardless of geographical location, vulnerable and others not.[20]

Sex Selection or "family balancing"?

The use of cfDNA screening for sex selection is another frequently cited concern in areas with a cultural preference for males, since it may exacerbate already skewed demographic trends.[23] It is illegal to disclose fetal sex information from any form of prenatal screening, including cfDNA screening, in China and India, but women and families continue to find ways to access this information. Demographic trends in India and China suggest that despite legal prohibitions, male births continue to outnumber female births and cfDNA will provide another mechanism to gain fetal sex information earlier in pregnancy.[23] For those who can afford it, flying to the United States or the United Kingdom for testing, or traveling across the border from China to Hong Kong, can circumvent such regulations.

By contrast, sex selection in the United States is available as a reproductive option to prospective parents under the more palatable label of "family balancing". "Family balancing" is presented as an option when there is an "unequal representation of genders among siblings" and aims to enable a "more balanced representation of both genders in a family".[2], 24 By framing parental preference for a particular sex as an expression of reproductive autonomy, the possibility that "family balancing" may still be motivated by ethically problematic biases regarding gender and sex is sidestepped. The use of sex selection for "family balancing" will not necessarily have such motivations and the adverse demographic effects will vary geographically depending on the strength of cultural pressures in favor of males. However, the juxtaposition of the concepts of "family balancing" with "sex selection" highlights the extent to which "Western" versus "non-Western" modes of thinking may obscure the ways in which similar issues appear cross-culturally.

Different thresholds for Disability: socio-economic and cultural influences

The relationship between prenatal testing and disability is complex and contentious. Disability rights activists argue that prenatal screening and termination of "affected" fetuses could ultimately lead to fewer resources being made available for those individuals living with screenable conditions, especially as birth rates of affected individuals decrease.[25] Movements that advocate for protections for, and recognition of, those with disabilities are stronger and better-resourced in more affluent communities in North America and Europe, facilitated in part by higher per capita income and the availability of organized social services. Contexts in which socioeconomic circumstances are strained generally provide less social and economic support for individuals with disabilities and their families, and fewer clinical options for women who receive a prenatal diagnosis. For example, women in urban centers will have more access to support services than those in rural areas.[26, 27, 28] Without extensive social support systems, termination may be the only viable reproductive option even when women/families may be willing to, or desire to, raise a child with special needs.

The thresholds of "disability" that are considered "socially acceptable" vary tremendously. For example, in India, concerns about marriageability and reproduction cause tremendous stigma for women carriers of X-linked disorders (which can affect either sex) and often lead to abortion of female fetuses that are carriers. Chile, by contrast, has the highest proportion of live Down syndrome births in the world (2.5/1000). Because abortion prohibitions are absolute, aborting on the basis of a Down syndrome diagnosis is very rare and children with Down syndrome are highly visible and well-integrated in Chilean society.[29] In Israel, the personal and social pressure to produce healthy, even "perfect," babies can be so severe that the threshold for termination is far lower.[30] In South Africa, the importance of fertility - given the religious, social, economic and political climate (including high HIV infection rates) - may encourage birth over selection of particular fetuses.[31]

Varying social norms thus create different types and levels of pressure on women and families when it comes to decision-making regarding testing and termination. It remains unclear how global variation in attitudes toward disability, combined with the widening

[2]Sex selection can also be used to avoid certain sex-linked disorders but it is not referred to as family balancing in this context.

array of new “conditions” tested by cfDNA screening, will unfold. In prior prenatal testing regimes, additional conditions were added or recommended for pregnancies known to be at specific familial risk of relatively rare conditions. Now, new panels are added as a bid for market share, opening up the possibility for an increasing number of conditions detectable by cfDNA screening to become labeled as a “disease” or “disability”. How might alternative notions of disability, local social support, and kinship networks affect what is considered a “disability” versus part of natural human variation? Recognizing the changing and locally situated nature of what is considered a disability suggests complex ethical and policy challenges regarding the best ways of adapting the implementation of cfDNA screening to local contexts. This is the case both in terms of what may be considered a “disability” in different cultural contexts and how individuals born with certain conditions may be affected by specific local circumstances that prevent access to or do not provide resources and support.

Prevalence of Genetic Conditions: Beyond Down syndrome

In some countries, aneuploidies such as Down syndrome are relatively low on the list of health priorities, if they are present at all. Genetic diversity and differences in disease prevalence, for example, make the hemoglobinopathies a far greater health priority than Down syndrome in regions of Africa, the Middle East and the Indian Subcontinent; prior efforts to encourage premarital screening/counselling have not been particularly effective at reducing the disease burden of hemoglobinopathies.[3] The potential to offer a relatively risk free and accurate screening tool for the hemoglobinopathies with cfDNA screening is therefore highly desired in many regions of the world and may provide far more significant public health benefits than aneuploidy screening.[32]

The fact that cfDNA screening is primarily aimed at detecting Trisomy 21 (and other trisomies) is a reflection of culturally specific prenatal health concerns present in North America and Europe, where Down syndrome has been the primary focus of prenatal screening programs for many years. One could imagine that had cfDNA screening originated in another context, it would be aimed at detecting other disorders, such as hemoglobinopathies, that are much more relevant in many regions of the world. The rapid globalization of a prenatal technology that detects conditions highly relevant in some places, and not others, illustrates how culturally bound values and priorities may be built into the very technology itself.

Economic realities

Economic realities fundamentally shape the way cfDNA screening is used, both by individual families and healthcare systems. Many national and regional healthcare systems are a complex mix of private and public institutions and payers. With a few exceptions in North America (some US State Medicaid and some private insurers will reimburse for cfDNA screening and the Health Systems of two Canadian Provinces have recently decided to include it) and Europe (such as Switzerland), cfDNA screening has been primarily

[3]Cyprus and Iran are exceptions and have successfully reduced the incidence of hemoglobinopathies through education, premarital, and prenatal screening programs.[32]

accessible through the private sector to those who can afford to pay out-of-pocket. In many regions, there is no third-party payer access to pregnancy care at all. To the extent that women access prenatal care in these regions, it is generally available through out-of-pocket pregnancy "packages". Families can purchase a bundle of prenatal services that include options such as regular ultrasounds, private versus public birthing rooms, and epidural pain relief. It is possible that cfDNA might find a place in such packages, which are generally offered by individual hospitals based on the resources available. However, the average price for cfDNA reported in Mainland China was approximately $330 to $472 USD in 2014. The median monthly household income in China in 2013 was approximately $515 USD, suggesting that cfDNA screening is out of reach for many families.[10] It is likely that in other areas, including Africa and India, these income disparities are even higher. This reality raises serious concerns regarding equity of access and the burden on women who are the most impoverished and vulnerable. Not coincidentally, these populations are also those that are likely to struggle the most with the resources to raise a child with a disability or disease.

Although prices may decrease over time, the current high cost of cfDNA screening makes it impractical to include in many public healthcare systems. Limited equipment and materials, non-existent or widely dispersed laboratory services, large rural populations, high perinatal and infant mortality rates, and burden of genetic diseases (e.g beta thalassemia) also affect the implementation and potential benefits of cfDNA screening. In many regions, women present late for prenatal care and alternative prenatal screening options - such as second trimester serum screening or ultrasound - are cheaper or fully covered and more practical than cfDNA screening. Getting women into clinics for necessary HIV screening, vitamin provision, and other basic prenatal services already strains available public health resources; comparatively expensive tests like cfDNA screening are beyond local capacity.

These realities are telling. Media and investment reports of the profit potential of cfDNA screening claim that "the global market for prenatal diagnostics in 2010 was USD 5.35 billion and it is expected to grow with an annual growth rate of 4.35% and generate revenues of USD 5.89 billion by 2018. The U.S. is the market leader in prenatal diagnostics followed by Europe. The market is expected to grow in the economies of Latin America and Asia Pacific."[33] Presumably, the considerable investment in cfDNA technologies is based on the assumption that part of this growth will be driven by an expansion in uptake of cfDNA screening. However, approaching this expansion from a relational and nuanced perspective suggests alternate understandings of how women and families make choices and value different information in the prenatal period. For instance, growth estimates are based on the global number of pregnancies and the increasing availability of cfDNA screening. Yet they are unlikely to take into account the realities women face in the global context. If families are in a position to choose between cfDNA screening and more essential pregnancy care, it is unclear what they will choose.

For example, national health services in some African countries *could* implement universal cfDNA screening, and thus create millions of cfDNA customers, but given choices between neonatal sickle cell screening and cfDNA screening for Down syndrome, it is unlikely that cfDNA screening represents the most efficient health expenditure. A commercial perspective regarding cfDNA screening that sees only "markets" and "consumers" ignores the socio-

cultural and public health context as well as the economic reality in which these supposed consumers are embedded. In a US context, the choice is often framed as a simple three way selection - based on patient preference - between serum screening, cfDNA screening, and invasive testing (amniocentesis or CVS). In a low and middle income context, by contrast, there are additional layers of economic complexity that make the concept of a simple trade-off unrealistic.

Impact of Commercialization on Ethical Care

The commercial provision of cfDNA screening distinguishes it from other forms of prenatal screening and diagnostic testing.[34] The economic drive to increase prenatal screening uptake, sometimes without adequate validation studies and in advance of professional guidelines or regulatory frameworks, is cause for concern.[35, 36] In some resource-limited regions, companies have been known to send nurses directly to patient homes to draw blood samples for cfDNA screening and genetic counselling is often provided by laboratory personnel. There may be a lessening of trust in health professionals in areas where financial ties between doctors and commercial companies are especially suspect, and in the context of rumors regarding companies bribing doctors to recommend and perform cfDNA screening.[12] Attempts to market cfDNA screening directly to consumers (DTC) in regions of India met with resistance and have been banned, but this has not prevented companies from marketing directly to non-specialist health providers.

Since 2015, cfDNA panels have also been expanding, first to include sex chromosome aneuploidies and then to encompass a variety of subchromosomal abnormalities such as microdeletion syndromes. The inclusion of increasingly rare conditions in cfDNA panels will inevitably increase the false positive rate of cfDNA screening, potentially limiting the primary benefit of cfDNA screening in reducing the need for diagnostic testing.[37, 38] This may be especially problematic in low resource areas with limited access to the skilled diagnostic practitioners required to confirm cfDNA results. Significant differences exist between these newly added conditions and the currently-screened trisomies, leading some to argue that highly disparate clinical realities are now being inappropriately lumped together and raising additional challenges to patient counseling.[11]

The aggressive global marketing of cfDNA screening increases pressures on both healthcare providers and women to use the technology, even in contexts where it may be clinically inappropriate or a misallocation of healthcare resources. Since cfDNA screening is mostly available by paying out of pocket, this could ironically increase pressure for middle class women in resource poor areas to sacrifice limited available resources for this new and aggressively marketed technology. Marketing materials that emphasize the strengths of cfDNA over the limitations and imply that cfDNA screening is “the best thing for the baby” encourage families to prioritize cfDNA screening over other health care decisions that may be more practical or desirable in the individual context. This is yet another reminder of the complex ways in which women may be differentially vulnerable.[20]

Informational needs and Resources

Existing professional guidelines (originating in North America and Europe) repeatedly emphasize the need for pre- and post-test genetic counselling to ensure women fully understand cfDNA screening and its limitations, but there are not enough genetics professionals to meet the increasing need.[6] For instance, South Africa–where 5000 cfDNA screening screens have been performed since 2013–currently has 1 geneticist for every 4.9 million individuals, 1 genetic counsellor for every 8.4 million, and 1 medical technician for every 21 million.[39] Nigeria reportedly has one maternal fetal medicine specialist trained in prenatal diagnosis for a population of over 188 million.[39] In Alaska there are no registered medical geneticists and Wyoming has only one genetic counselor to serve over half a million.[11, 40] Thus, in many regions of the world, the burden of administering cfDNA screening often falls to non-specialist health care providers, such as primary care doctors, obstetricians, nurses, midwives, and community health workers, many of whom are underprepared to mediate the appropriate use of cfDNA screening and counsel patients regarding its capabilities and limitations.

The shortage of counselling and informational resources has important clinical and ethical implications that are being felt globally. One especially concerning element is ongoing confusion over the diagnostic capabilities of cfDNA screening. Evidence suggests there is global confusion among patients and providers interpreting cfDNA screening results, even where expertise is more widely available. Reports have emerged in the mass media of women in the US very nearly, or actually, aborting fetuses based on an cfDNA screening result without confirmatory testing - sometimes based on incorrect guidance from doctors- or giving birth to babies affected with conditions about which they were falsely reassured by a “negative” cfDNA screening result.[41] A large US-based study found that 6% of participating women terminated their pregnancies based on a cfDNA screening result without diagnostic confirmation and it is unclear what advice, if any, these women received from health care providers.[42]

While genetic counselors, specialists in maternal fetal medicine, and obstetric providers may be well placed to interpret cfDNA screening results, many healthcare providers are not. Meanwhile, the vast majority of prenatal care worldwide takes place outside of secondary or tertiary medical centers that employ specialist expertise. At the same time, the continued insistence by professional guidelines that genetic counseling or other expertise is required to ensure adequate informed consent neglects the fact that in some regions (such as India) experienced social and community health care workers may have the prior experience and close ties with communities needed to effectively counsel women and families about relevant genetic disorders and prenatal screening. Thus, social and national context does not obviate the need for accurate information and decisional support in making prenatal care decisions, but it does impact the best ways in which such support may be provided. Given the realities of medical care in many regions, it may be more effective for professional guidelines to emphasize the *actual information* with which families need to be provided rather than referring the discussion to specialist providers who do not exist.

Conclusion

Normative frameworks regarding the provision of prenatal screening that originate and reflect North American and European ethical priorities – such as reproductive autonomy and procreative freedom - may distract attention from essential elements of local context. The utility and ethical implications of cfDNA screening are highly variable and dependent upon local healthcare systems, cultural, economic, and sociopolitical contexts and needs. This paper illustrates that many of the often-cited benefits - such as earlier availability and higher sensitivity to trisomy - have variable value depending on the setting. As cfDNA screening expands, we must remain attuned to the variability and dynamism between cultures, religions, nations, and communities, which belie generalization. The broad spectrum of sociocultural attitudes towards disability, gender, genetic diversity, economic constraints, and disease prevalence significantly shape the ways cfDNA screening is perceived and the benefits it may or may not provide. Remaining attuned to variabilities in local context also acts as an essential reminder that many of the ethical concerns arising from cfDNA screening are present in varying guises in all places, including North America and Europe. Engaging with socio-cultural diversity can facilitate ethically-sensitive implementation of cfDNA screening and inform appropriate health policy. Fostering appropriate roll-out of this “simple blood test” requires close attention to the interaction of technology and the complex environment in which it is implemented.

References

1. Benn P, Cuckle H, Pergament E. Non-invasive prenatal diagnosis for Down syndrome: the paradigm will shift, but slowly. Ultrasound in Obstetrics & Gynecology. 2012; 39(2):127–30. http://onlinelibrary.wiley.com/doi/10.1002/uog.11083/abstract. DOI: 10.1002/uog.11083/abstract [PubMed: 22278776]
2. Bianchi D, Parker RL, Wentworth J, et al. DNA sequencing versus standard prenatal aneuploidy screening. NEJM. 2014; 370:799–808. [PubMed: 24571752]
3. Bianchi DW, Wilkins-Haug L. Integration of Noninvasive DNA Testing for Aneuploidy into Prenatal Care: What Has Happened Since the Rubber Met the Road? Clin Chem. 2014; 60:78–87. [PubMed: 24255077]
4. Clinical NGS Market in China Poised to Take Off as China FDA Looks to Establish Guidelines. Sep 18. 2015 GenomeWeb. April 2016, at: https://www.genomeweb.com/sequencing-technology/clinical-ngs-market-china-poised-take-china-fda-looks-establish-guidelineshttps://www.genomeweb.com/sequencing-technology/clinical-ngs-market-china-poised-take-china-fda-looks-establish-guidelines
5. Minear MA, Lewis C, Pradhan S, Chandrasekharan S. Global perspectives on clinical adoption of cfDNA screening. Prenat Diagn. 2015; 35:959–67. [PubMed: 26085345]
6. Dondorp W, de Wert G, Bombard Y, et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Eur J Hum Genet. 2015; 23:1438–1450. Available from: http://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg201557a.htmlhttp://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg201557a.html. [PubMed: 25782669]
7. Agarwal, Ashwin, Sayres, Lauren C., Cho, Mildred K., Cook-Deegan, Robert, Chandrasekharan, Subhashini. Commercial Landscape of Noninvasive Prenatal Testing in the United States. Prenatal Diagnosis. 2013; 33(6):521–31. [PubMed: 23686656]
8. Farrell RM, Mercer MB, Agatisa PK, Smith MB, Philipson E. It’s More Than a Blood Test: Patients’ Perspectives on Noninvasive Prenatal Testing. J Clin Med. 2014 Jun 19; 3(2):614–31. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4449684/. [PubMed: 26237393]
9. Chetty S, Garabedian MJ, Norton ME. Uptake of noninvasive prenatal testing (NIPT) in women following positive aneuploidy screening. Prenat Diagn. 2013 Jun 1; 33(6):542–6. Available at :

http://onlinelibrary.wiley.com/doi/10.1002/pd.4125/abstracthttp://onlinelibrary.wiley.com/doi/10.1002/pd.4125/abstract. [PubMed: 23592525]

10. Chandrasekharan S, Minear MA, Hung A, et al. (2014) Noninvasive prenatal testing goes global. Sci Transl Med. 2014; 6:231fs15.
11. Allyse M, Minear MA, Berson E, et al. Non-invasive prenatal testing: a review of international implementation and challenges. Int J Wom Health. 2015; 7:113–26.
12. Minear MA, Lewis C, Pradhan S, Chandrasekharan S. Global perspectives on clinical adoption of cfDNA screening. Prenat Diagn. 2015; 35:959–67. [PubMed: 26085345]
13. Haidar H, Rispler-Chaim V, Hung A, et al. Non-Invasive Prenatal Testing: Implications for Muslim Communities. AJOB Empirical Bioethics. 2015; 6:94–105.
14. Non-Invasive Prenatal Testing in the Non-Western Context Meeting. Brocher Foundation; Dec 14–17. 2015 October 2016, at: http://www.brocher.ch/fr/events/165/non-invasive-prenatal-testing-in-the-non-western-context
15. Mackenzie, C., Stoljar, N. Relational Autonomy: Feminist Perspectives on Autonomy, Agency, and the Social Self. Oxford University Press; 2000.
16. Jennings B. Reconceptualizing Autonomy: A Relational Turn in Bioethics. Hastings Center Report. 2016; 46(3):11–6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/hast.544/abstract.
17. Moazam F. Feminist Discourse on Sex Screening and Selective Abortion of Female Foetuses. Bioethics. 2004 Jun 1; 18(3):205–20. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1467-8519.2004.00390.x/abstracthttp://onlinelibrary.wiley.com/doi/10.1111/j.1467-8519.2004.00390.x/abstract. [PubMed: 15341033]
18. van den Heuvel A, Chitty L, Dormandy E, Newson A, Attwood S, Ma R, et al. Is informed choice in prenatal testing universally valued? A population-based survey in Europe and Asia. BJOG: An International Journal of Obstetrics & Gynaecology. 2009; 116(7):880–5. http://onlinelibrary.wiley.com/doi/10.1111/j.1471-0528.2009.02174.x/abstract. DOI: 10.1111/j.1471-0528.2009.02174.x/abstract [PubMed: 19522793]
19. Otaño L, Igarzábal L. Noninvasive Prenatal Testing for Fetal Aneuploidy in Argentina. AJOB Empirical Bioethics. 2015; 6(1):111–114.
20. Luna F. Elucidating the concept of vulnerability: Layers not labels. International Journal of Feminist Approaches to Bioethics. 2009; 2(1):121–39.
21. Guttmacher Institute. Apr. 2016 at: http://www.guttmacher.org/statecenter/spibs/spib_OAL.pdf
22. Dervan, AP., Deverka, PA., Trosman, JR., Weldon, CB., Douglas, MP., Phillips, KA. Payer decision making for next-generation sequencing-based genetic tests: insights from cell-free DNA prenatal screening. Genet Med. 2016. Available from: http://www.nature.com/gim/journal/vaop/ncurrent/full/gim2016145a.html
23. Madan K, Breuning MH. Impact of prenatal technologies on the sex ratio in India: an overview. Genet Med. 2014 Jun; 16(6):425–32. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052431/http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4052431/. [PubMed: 24177057]
24. Genetics & IVF Institute. Apr. 2016 at http://www.givf.com/familybalancing/
25. Kaposy C. A disability critique of the new prenatal test for Down syndrome. Kennedy Inst Ethics J. 2013 Dec; 23(4):299–324. [PubMed: 24552074]
26. Devlieger, P., Rusch, FR., Pfeiffer, D. Rethinking Disability: The Emergence of New Definitions, Concepts and Communities. Amsterdam: Garant Uitgevers N V; 2003.
27. Ingstad, B., Whyte, SR. Disability in Local and Global Worlds. Berkeley: Univ California Pr; 2007.
28. Gammeltoft, T. Haunting Images: A Cultural Account of Selective Reproduction in Vietnam. Berkeley: Univ California Pr; 2014.
29. Nazer HJ, Aguila RA, Cifuentes OL. Increasing rates of Down syndrome among newborns in Chile from 1972 to 2005. Rev Med Chil. 2006 Dec; 134(12):1549–57. [PubMed: 17277872]
30. Ivry, T. Embodying Culture: Pregnancy in Japan and Israel. Rutgers University Press; 2011.
31. Dyer SJ, Abrahams N, Hoffman M, van der Spuy ZM. 'Men leave me as I cannot have children': women's experiences with involuntary childlessness. Hum Reprod. 2002; 17(6):1663–8. Available

from: http://humrep.oxfordjournals.org/content/17/6/1663http://humrep.oxfordjournals.org/content/17/6/1663. [PubMed: 12042295]

32. Cousens NE, Gaff CL, Metcalfe SA, Delatycki MB. Carrier screening for Beta-thalassaemia: a review of international practice. Eur J Hum Gen. 2010; 18(10):1077–1083. DOI: 10.1038/ejhg.2010.90
33. Prenatal Diagnostics Market - Global Industry Size, Share, Trends, Analysis And Forecast 2012–2018. Transparency Market Research. Apr. 2016 at http://www.transparencymarketresearch.com/prenatal-diagnostics-market.htmlhttp://www.transparencymarketresearch.com/prenatal-diagnostics-market.html
34. Allyse M, Chandrasekharan S. Too much, too soon?: Commercial provision of noninvasive prenatal screening for subchromosomal abnormalities and beyond. Genet Med. 2015 Mar 19. Advanced online publication. doi: 10.1038/gim.2015.23
35. Mozersky J, Mennuti MT. Cell-free fetal DNA testing: who is driving implementation? Genet Med. 2013; 15(6):433–4. Available from: http://www.nature.com/gim/journal/v15/n6/full/gim2012156a.html. [PubMed: 23222661]
36. Blake, Murdoch, Vardit, Ravitsky, Ubaka, Ogbogu, Sarah, Ali-Khan, Gabrielle, Bertier, Stanislav, Birko, Tania, Bubela, Jeremy, DeBeer, Charles, Dupras, Meika, Ellis, Palmira, Granados Moreno, Yann, Joly, Kalina, Kamenova, Zubin, Master, Alessandro, Marcon, Mike, Paulden, Francois, Rousseau, Timothy, Caulfield. Non-Invasive Prenatal Testing and the Unveiling of an Impaired Translation Process. J Obstet Gynecol Canada. 2016 in press.
37. Lo, KK., Karampetsou, E., Boustred, C., et al. Limited Clinical Utility of Non-invasive Prenatal Testing for Subchromosomal Abnormalities. Am J Hum Genet. 2015. Corrected Proof. available online. DOI: http://dx.doi.org/10.1016/j.ajhg.2015.11.016http://dx.doi.org/10.1016/j.ajhg.2015.11.016
38. Ravitsky V, Laberge Rousseau F. Providing unrestricted access to prenatal testing does not translate to enhanced autonomy. AJOB. 2016 In press.
39. Figures provided during presentation by a workshop participant.
40. National Society of Genetic Counselors. Oct. 2016 at http://nsgc.org/p/cm/ld/fid=164
41. Daley, B. Oversold prenatal tests leading to abortions. The Boston Globe. 2014 Dec 14. Available from: https://www.bostonglobe.com/metro/2014/12/14/oversold-and-unregulated-flawed-prenatal-tests-leading-abortions-healthy-fetuses/aKFAOCP5N0Kr8S1HirL7EN/story.htmlhttps://www.bostonglobe.com/metro/2014/12/14/oversold-and-unregulated-flawed-prenatal-tests-leading-abortions-healthy-fetuses/aKFAOCP5N0Kr8S1HirL7EN/story.html
42. Dar, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. Am J Obstet Gynecol. 2014; 211:527. [PubMed: 25111587]