Received: 26 February 2019 | Revised: 6 May 2019 | Accepted: 30 May 2019

DOI: 10.1002/pd.5495

ORIGINAL ARTICLE

WILEY PRENATAL DIAGNOSIS

Pandora's pregnancy: NIPT, CMA, and genome sequencing—A new era for prenatal genetic testing

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Funding information
Deutsche Forschungsgemeinschaft

Abstract

Objectives: We delineate in this article a shift from the "traditional" technologies of karyotyping in PND to the current phase of advanced genetic technologies including noninvasive prenatal testing (NIPT), chromosomal microarray analysis (CMA), and whole-exome sequencing (WES) with their higher detection rate and related abundance of uncertain data.

Methods: Conceptual analysis based on seminal works that shaped the socioethical discourse surrounding the experiences of parents as well as professionals with prenatal diagnosis in the last 30 years.

Results: We consider the implications of this new era of PND for patients and health professionals by drawing on previous studies documenting how probability and uncertainty affect informed consent/choice, health risks communication, customer satisfaction and decision making, and parent-child bonding.

Conclusions: We argue that these changes move us beyond the idioms and realities of the tentative pregnancy and moral pioneering, to uncertainty, probability-based counseling, and moral/translational gambling. We conclude by discussing what is needed to maintain hope in the era of Pandora's pregnancy.

1 | INTRODUCTION

The new technologies of prenatal genetic diagnosis (PND) mark a watershed of change fueled by growing commercialization and abundance of information (often in the form of probabilities and chance), joining and augmenting previous torrents of anxiety, tentativeness, and hard moral decisions. We argue that while there are prospects and perils that have been in the field of PND all along, now, there are more challenges involving very complex risk information and communication, exacerbating previously existing issues.

In our time, more people get more information and options for prenatal testing. Yet, information and knowledge are not the same. While information is processed data about something, knowledge is filtered information made relevant and useful for the subject. As a result, at least two main trajectories open up. On the one hand, many people are satisfied with knowing that the result is negative, find it beneficial to know a positive result, or even feel capable of dealing with the information overload. On the other hand, many users are faced with an odyssey of testing, with one test leading to another (eg, serum screening leading to noninvasive prenatal testing [NIPT], leading to amniocentesis), with an uncertainty that is paradoxically increased by testing (eg, the detection of VUS—genetic variants of uncertain clinical significance), or with the risk of "being at risk" (a murky diagnosis that sometimes lingers for years after birth). While certain risks—such as those related to miscarriage—may decrease following noninvasive procedures, we focus here on the general experience of the "risk of being at risk," arguing that its growing presence has become a critical new landmark of this era of PND, as more information needs to be considered.

In what follows, we will not return to the broad questions of enhancement, eugenics, or designing of future generations, all

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

extensively studied ethical and social issues in this field. Our commentary will follow another strand of scholarly work, focusing on the experiences of professionals and expecting parents, mainly, of course–pregnant women, ever since the introduction of amniocentesis as an increasingly common prenatal diagnostic test during pregnancy, in the 1970s.

In the following, we distinguish two phases in the development of the field. First, we focus on seminal works that provided key metaphors for the initial era. Second, we discuss the current era that we suggest calling "Pandora's pregnancy," based on former studies,[1,2] which used Pandora's box as a metaphor for what lurks in advanced prenatal genomic tests. We substantiate our claim through a meta-analysis of seminal studies concerning the experiences of parents as well as of professionals with PND.

What's already known about this topic?

- Prenatal diagnosis is known to transform the experience of pregnancy. Present-day technologies offer higher detection rate and related abundance of uncertainty, increasing the complexities involved in interpreting test results.

What does this study add?

- It distinguishes two phases in the development of the field.
- It summarizes former discussions and offers a new conceptual analysis of the current phase.
- It argues that the current "Pandora's pregnancy" era calls for nondeterministic counselling and an acknowledgment of the moral/translational gambling experience, complicating the ability to provide patients with information that they will find helpful.

2 | FIRST STAGE—THE TENTATIVE PREGNANCY, MORAL PIONEERING, AND GENETICIZATION

Katz-Rothman,[3] as early as 1986, and Rapp[4] in 1999, wrote the most classical works about this then new medical experience of pregnancy at the age of the diagnosable embryo/fetus. At the early days of amniocentesis, Katz-Rothman suggested that mothers were expected to see their children as products in the making, which have to be carefully examined for quality control before leaving "the factory." Some critical sociological and feminist scholars then saw this as part of the general process of the commodification of the human/female body in late capitalism. Katz-Rothman[3] further claimed that what were then new medical tests posed contradictory demands on women, to love their child and take care of it from the moment of conception, but also to be willing to abort it in case a genetic problem was detected. Hence, she coined the term "tentative pregnancy" to describe this ambivalence.[3]

Thirteen years later, in 1999, Rapp used the term "moral pioneers" to complement the description of modern pregnant women's emotional and cognitive morass. Situated in the research frontier of the expanding capacity for PND, Rapp described future mothers as forced to judge the quality of their fetuses and to make concrete and embodied decisions about their own motherhood and the standards for entry into the human community. But how were they to judge? What medical information were they faced with?

Technology of stage 1 was mainly karyotyping. While it did not produce black and white predictions about the child's future health and characteristics, as diagnosable conditions always varied based on severity, penetrance, and treatment availability, it produced far less information than stage 2 (current) technologies. While counselees might have construed results concerning chromosomal conditions as binary—either positive or negative—prenatal karyotyping also had its share of uncertainty.[5]

While there are studies estimating the morbidity risks associated with certain chromosomal rearrangements identified via karyotyping,[6] it is hard to find studies indicating a general number representing the overall prevalence of uncertain findings found in karyotyping. This is in contrast to the well-documented incidence of findings of uncertain significance in the new methods (for instance, a prevalence of approximately 1%-2% of VUS in CMA[7-9]). We could not find large-scale studies explicitly comparing karyotyping and CMA with regard to the prevalence of findings with uncertain clinical significance, let alone when both methods were used on the same fetal samples. However, a study based on a smaller cohort demonstrates a much higher incidence of such findings detected on CMA compared with karyotyping, and the difference between the methods is dependent on the resolution of the CMA used.[10] In light of the aforementioned, we cannot determine the precise increase in uncertain findings between karyotyping and current methods. Yet such an increase apparently goes hand in hand with the higher resolution and abundance of data that are the hallmarks of the current era, as demonstrated in new generation sequencing methods.[11] The epitome of this increase is arguably the new term "variants of uncertain significance" (VUS), which had not existed previously in the context of karyotyping and the many debates regarding communicating such information to users of the new technologies. It is apparent that the issue of uncertainty appears much more often in the literature on new generation methods compared with karyotyping and that it is central to current discussions in the field. The discourse has shifted and now focuses much more on uncertainty—both in terms of test performance, ie, indicating numbers, and in terms of its implications, ie, the role uncertainty plays in clinical routines and its impact on professionals and users.

Notwithstanding karyotyping's share of uncertainty, in the 90s, it became common for sociologists of medicine to criticize PND as reductionist, essentialist, and deterministic. Lippman[12] had coined the term "geneticization" (1991) to criticize the hope and hype of reassurance, choice, and control provided by PND. Geneticization also addressed the false understanding of genetics among policy makers, the public, and the media whose views of genetics were considered too simplistic. Another strand of important criticism came from the

disability advocacy critique[13,14] as well as from feminist critics.[15] By now, we believe that the "DNA mystique"[16] of the 90s has faded away, as it is quite generally understood that we are not simply our genes. But how does this effect the experience of pregnancy? Can it be that to know more, and to be aware of complexity, is sometimes to know less?

3 | SECOND STAGE: PANDORA'S PREGNANCY

3.1 | Increasing the variety of PND

With the increasing variety of PND methods (see Figure 1), choices are often illusory, since new technologies imply a social moral duty toward uptake.[17]

Testing cell-free fetal DNA (cffDNA) circulating in the pregnant woman's blood is quite a recent innovation. The screening test known as NIPT requires just a blood test and can be performed starting week 9, hence providing results early in pregnancy. Although it is not considered diagnostic, unlike amniocentesis and CVS, it poses no risk of miscarriage, thus changing the balance of risk versus chances of detection of anomaly. The ease and lack of risk of NIPT may lead women to feel less justified in saying no to testing, since there is no longer an "excuse" to decline it.[18] Another major reason for its fast diffusion is the fact it is highly commercialized[19] and often pushed forward direct-to-consumer (DTC), potentially bypassing traditional professional barriers. The commodification process Katz-Rothman[3] discussed in the 80s mostly in the sense of the view of the human body as yet another capitalist commodity is accelerating in the most simplistic economic sense of profit-motivated companies, which are constantly taking a larger role in shaping the field of PND.

Year	Prenatal **genetic** diagnosis technology
1956	Amniocentesis first used to identify genetic disorders. Karyotyping first used to identify trisomy 21 as cause of Down syndrome
1983	Chorionic villus sampling (CVS) first performed
2010	First use of Chromosomal Microarray Analysis (CMA) for analysis of samples obtained from amniocentesis or CVS
2011	Cell free DNA screening tests (known as NIPT) first clinically available. They analyze fragments of placental and fetal DNA circulating in pregnant woman's blood to assess fetal sex and the likelihood of Trisomy 13, 18 or 21, as well as microdeletions and microduplications.
2013	NIPT available commercially
2013	The ACMG recommends that WES be considered when specific genetic tests for a phenotype fail to determine a diagnosis in a fetus with multiple anomalies suggestive of a genetic disorder
2017	Noninvasive whole genome sequencing (WGS) is technically possible but is not yet commercially available in the prenatal context

FIGURE 1 Evolution of prenatal genetic testing (based on the Hasting's Center report, https://www.thehastingscenter.org/prenatal/evolution-prenatal-testing/)

For many future parents, NIPT is reassuring, given the high performance of the test (especially in the detection of trisomy 21), ie, its lower rates of false-positive and false-negative results, compared with traditional biochemical screening tests.[20] Yet NIPT may still involve false-positives, which imply further testing, as well as false reassurance in the form of false-negatives (rates of FP and FN require clinical follow-up and therefore vary by research, location, product, and medical condition). Continuing the disability critique of the "old" turn-of-the-century PND, NIPT has also been opposed as eugenic by disability activists in Europe.[21,22]

Nowadays, NIPT is not replacing the traditional diagnostic amniocentesis/CVS, which are expanded by Chromosomal Microarray Analysis (CMA, see Figure 1). Rather, in case of an abnormal test result, NIPT leads to further diagnostic tests, as recommended by the ACMG.[23]

In the future, it is predicted that NIPT will be merged with contemporary advances in molecular genetics to allow detailed investigations of the fetal genome. It is probable that such tests will become accessible or even routinized for a large number of women in the general population, most of whom at "low-risk," as is already the case in the Netherlands.[24] This will form a dramatic change in the quantity of pregnant women having to face the unique dilemmas of these tests, discussed in the following.

3.2 | Future parents' experiences

CMA, whereby small gains and losses of genetic material are identified, has become the recommended first-line genetic investigation in pregnancies with fetal abnormalities detected in ultrasound.[25] A growing number of centers are offering CMA to all women undergoing amniocentesis and CVS. Some claim that CMA should be performed in prenatal diagnosis, instead of karyotyping, regardless of the clinical indication for testing.[26] Additionally, exome-sequencing whereby the encoding part of the genome is examined has been increasingly introduced in pregnancies with structural anomalies.[27,28]

The main benefit of advanced genomic diagnostic tests such as CMA and exome sequencing is their higher detection rate compared with karyotyping. They produce much more genetic data with much higher resolution. Nevertheless, the higher resolution in which the genome is examined has its downsides as well. These tests are usually not meant to look for a known risk variant. Rather, more like throwing a fishing net into the sea, they are scanning the whole "genomic ocean" waiting to see what comes up. Furthermore, they are often not executed due to a condition established following examination of the phenotype. In many cases, it is the genotype and not the phenotype that leads the process. As a result, finding a genetic variant (where the reference point for variation is genomic rather than phenotypic) may have no currently determined significance. Thus, detection of a genetic "aberration" in contemporary methods has become far more common, complex, and open to interpretations and reclassification as either benign or pathogenic. Only in some of the cases can a definite diagnosis be reached.

The challenging nature of VUS is the result of limited data concerning these variants, or because of variable phenotypes associated with them.[25] Therefore, it is a common event that probabilistic rather than deterministic information is reached. Such findings are obviously stress factors for parents and professionals, as knowledge has brought along increasing uncertainty.[29,30] For example, Werner-Lin et al[17] found that couples describe being thrown into a state of crisis, due to the gap between their expectations before testing and their actual confrontation with the test's limitations. Reactions to uncertain test results were strong, to the point where women described the gained information as "toxic" and regretted having it.[31] Similar trends of uncertainty-related stress were found in CMA testing performed postnatally.[32] Moreover, this uncertainty may stigmatize the fetus and cause anxiety and overdiagnosis during pregnancy and possibly post birth. Genetic knowledge, like all medical knowledge, was never completely certain. Nonetheless, current tendencies force future parents to increasingly deal with probabilistic knowledge, and uncertainty may take its toll affecting parent-child bonding also in the long run, as some parents report ongoing worry and constant looking for signs of abnormal development of their child, linked to the detected uncertain finding. This includes turning to medical evaluation and intervention even without apparent health problems.[33] Similar concerns were shared by parents with regard to disclosing prenatally detected susceptibility loci (SL) (findings associated with an unquantifiable risk of neurodevelopmental disorders, with phenotypic heterogeneity and/or of variable expressivity). Therefore, participants presented their wish to be able to individually choose in the pretest setting whether or not to be informed of detected SL.[34] Such individualized choice in the form of opt-out possibility can support, according to the authors, reproductive autonomy.

Advanced genomic tests also increasingly lead to secondary findings, such as risks for adult-onset conditions.[35] This may also indicate that one of the parents has the same adult-onset disease but has not yet developed symptoms,[7] which can obviously benefit the parent as well as the wider family. However, a greater risk for developing, in the far future, common diseases such as heart disease or cancer, is very hard to think through. That is, since we are ignorant of our children's future life circumstances, will they live long enough to develop the disease? Will they be among the ones who do or do not develop it? What will be the severity of the condition, and what will future therapies look like?

What can a supposedly rational person/future parent make of such an "informed" "choice"? Knowledge is considered essential to allow informed uptake of tests and decision making in case of an abnormal finding. Yet is informed consent, that is, voluntary consent by a competent patient to whom full disclosure has been made, and who fully understands all that has been disclosed, still relevant in its "traditional," broad and one-off format?

In light of this abundance of uncertainty, we suggest terming today's future parents not just moral pioneers,[4] but moral gamblers, as parents understand that in some cases, whatever their decision, it is not based on definite medical facts.

Moreover, as van der Steen et al[36] argue, the quality of the decision-making process should be measured not solely by how much it was based on knowledge and understanding of the information, but equally on whether the decision reached is in consistency with the woman's values.

3.3 | Professionals' dilemmas

The new era of PND carries far-reaching implications not only for users but also for professionals as well. A study of pregnant genetic counselors showed that they too described genetic information as providing both a sense of control and a source of dilemmas and stress.[37] Of course, professionals are affected by the new technologies not only as patients themselves but also mainly as service providers. Due to the increase in informing parents of uncertain results and since patients do not respond well to uncertainty, professional-patient relationship is affected. Professionals described very angry reactions from patients when reporting uncertain findings.[38] The currently common situation, in which professionals cannot offer clear predictions, adds a nondeterministic principle to the traditional dictum of nondirectiveness. The ideal of nondirectiveness on its own has inherent ethical as well as practical complexities,[39] and the presently frequent addition of probabilistic information dramatically increases the challenge experienced by professionals. Studies have stressed that in order to minimize users' misunderstanding and frustration and to reduce tension between professionals and their patients, it is important to discuss with users their expectations from the tests and to emphasize their limitations before obtaining consent. However, especially in the new era of PND, this goal is considered difficult to achieve.[40,41]

Studies on professionals' views regarding advanced genomic tests demonstrate the complexities in communicating test results with users. The difficulties described fall within different areas including communicating test results to users; achieving informed consent; information overload; disclosing secondary findings; the level of users' freedom in deciding what information they wish to receive; and the lack of sufficient time/resources for a proper consultation.[1,38,40,42,43]

Furthermore, in the era of defensive medicine, minor uncertainties lead to a directive to disclose all information and to offer extra diagnostic tests, which are presented in order to protect the physician against the patient becoming a potential plaintiff, and not necessarily for her medical good.[44] Moreover, whereas professionals' ethical perspective highlights justice and beneficence/non-maleficence, lay groups emphasize autonomy and hence receiving all information.[2] The new technologies challenge the scope of professionals' responsibilities toward patients and their families. For instance, the reclassification of VUS calls for ethical, legal, and practical examination with regard to the responsibility of health professionals to recontact users and patients (and/or their at-risk relatives) whose interpretation of test results has changed.[45] Another obscurity relates to whether professionals have a responsibility toward a person who was tested while being a fetus. Whose responsibility is it to inform such people of their test results[1]?

4 | THE WAY FORWARD

When Pandora opened the jar, all evil escaped it, but then she also held hope inside the jar by closing the lid. By opening up the lid of pregnancy and inspecting the fetus through the growing variety of modern PND technologies, we also unleash complexity and uncertainty. This is Pandora's pregnancy. It adds new elements while continuing and amplifying old ones. As before, complex difficult decisions have to be reached during the delicate phase of pregnancy, a stressful physical and emotional situation, and under time pressure.

The old challenges have not lost their relevance. The tentative pregnancy and moral pioneering are still here, involving hard decisions, but not just about abortion. In addition to asking myself if I am willing to abort or raise a disabled child, now, an additional question involves translational pioneering: How to translate the abundance of information of variants and probabilities into lay phenomenology that can inform my decision. This also involves what we termed as moral gambling.

Pandora's pregnancy, as a new reality of advanced prenatal testing, is not alone. It demonstrates and joins other examples of the current implementation of personalized/precision genomic medicine, where patients and their families are placed in increasingly uncertain situations. In such settings, the sociopsychological burden of uncertainty is shifted to patients, with physicians (as well as human geneticists and genetic counselors) performing "bridging work" instead of managing users' or patients' complaints/expectations.[46] To maintain hope in the era of Pandora's pregnancy and provide users with information that they will find helpful, we need today new foci as well as more of the same emphases that were needed in the 90s, including (a) accounting for uncertainty in genetic counseling; (b) promoting reproductive choice rather than test uptake as the preferred measure of screening program's "success" (such concrete efforts should include balanced information, including on life with disability, presented in genetic counseling before testing); (c) educating health professionals about prenatal testing in the context of political and social issues related to disability; (d) promoting genetic literacy among users of PND; and (e) developing new counseling methods and allowing more time in order to provide a sensitive service, acknowledging the moral/translational gambling experience, which complicates the ability to provide patients with information that they will find helpful.

ACKNOWLEDGEMENT

None

CONFLICTS OF INTEREST

None declared.

FUNDING SOURCES

Grant of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). "Meanings and Practices of Prenatal Genetics in Germany and Israel: A Comparative Empirical and Prospective Study of the Views and Ethical Concerns of Users, Non-Users and Providers of Prenatal Genetic Services in Their Social and Cultural Contexts."

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How to cite this article: Hashiloni-Dolev Y, Nov-Klaiman T, Raz A. Pandora's pregnancy: NIPT, CMA, and genome sequencing—A new era for prenatal genetic testing. *Prenatal Diagnosis*. 2019;39:859–865. https://doi.org/10.1002/pd.5495