Published in final edited form as:

Prenat Diagn. 2019 April ; 39(5): 339–343. doi:10.1002/pd.5379.

Current Controversies in Prenatal Diagnosis 2: NIPT Results Suggesting Maternal Cancer Should Always Be Disclosed

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Introduction

(Diana W. Bianchi, Moderator)

Sequencing of cell-free DNA (cf-DNA) circulating in the plasma of pregnant women to screen for the common fetal autosomal aneuploidies is the first widespread implementation of genomic medicine.¹ It first became clinically available in 2011. As early as 2013, however, cases of “false-positive results” began to appear in the literature, in which the noninvasive prenatal screening test (NIPT) result reported aneuploidy, but the diagnostic fetal karyotype or chromosome microarray was euploid.² The underlying biological explanation for these discordant results appeared to be confined placental mosaicism or a twin demise. Maternal malignancy was not initially considered in the differential diagnosis, because cancer is estimated to occur in only 1 in 1000 pregnant women.³ When cancer occurs during pregnancy, the most common types are Hodgkin and non-Hodgkin lymphoma, breast, ovarian and cervical cancers, malignant melanoma, colorectal cancer and leukemia.³ In many of these malignancies, tumor DNA is shed directly into the circulation. This is the basis of the concept behind the liquid biopsy.⁴ Common, benign tumors such as uterine leiomyomas, also shed DNA into the bloodstream.⁵ The reason that the NIPT results are abnormal in the setting of maternal malignancy is that the tumor DNA contains multiple areas of duplications and deletions across the genome. This skews the expected ratios between patient and reference DNA, giving rise to test failures or unusual multiple aneuploidies, including monosomies, that would not be expected in a living fetus.

In 2013 the first case of a discordant NIPT result due to maternal metastatic disease was published⁶. The 37-year-old G2P1 woman underwent NIPT at 13 weeks of gestation. The result was abnormal, with trisomy 13 and monosomy 18 detected. A confirmatory amniocentesis revealed a normal male karyotype. The patient’s extensive clinical work-up is

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Conflicts of Interest: Peter Benn is a consultant to Natera, Inc.; Sharon Plon is on the scientific advisory panel of Baylor Genetics Laboratories; Diana Bianchi has no conflicts of interest.

This is a written summary of the oral debate presented on July 10, 2018 at the 22nd annual meeting of the International Society for Prenatal Diagnosis, held in Antwerp, Belgium. The opinions stated were assigned and do not necessarily reflect the personal or professional opinions of the authors.

described in the initial publication⁶ and in an interview.⁷ Her history was significant for the fact that after delivery of a healthy male infant, she experienced severe pelvic pain, which was determined to be due a pathologic pelvic bone fracture secondary to a metastatic neuroendocrine carcinoma. She was subsequently treated for her malignancy and is still alive five years post-partum. Another 37-year-old G2P1 woman who had cf-DNA test results suggesting full or partial monosomies of chromosomes 13, 18, 21 and X was not as fortunate.⁸ After an amniocentesis revealed a normal female karyotype (46, XX) and a normal chromosome microarray, the patient was referred to an oncologist. A full-body MRI scan without contrast at 23 weeks of gestation identified multiple T2 hyperintense and T1 hypointense lesions in the liver. Because the patient was clinically asymptomatic, the decision was made not to perform a biopsy. Over the next nine weeks the hepatic lesions grew; an elective cesarean delivery at 32 weeks was performed to facilitate maternal diagnosis and management. Her diagnosis was stage IV colon cancer. She did not respond to chemotherapy and died at 10-months post-partum. Results of two different NIPTs performed during pregnancy showed excess amounts of DNA sequence that mapped to chromosomes 7, 8, 10, 14 and 20 and triggered the bioinformatics algorithm to interpret the test results as multiple monosomies.

In 2015 Bianchi *et al.* performed a retrospective analysis of detailed clinical and genome-wide sequencing data from eight women who had NIPT results positive for one or more aneuploidies of chromosomes 13, 18, 21, or X, with a euploid fetus.⁹ In seven of the eight cases, maternal cancer occurred when there was more than one aneuploidy detected. Detailed bioinformatics analyses revealed unique patterns of nonspecific copy-number gains and losses across the genome that resolved after completion of treatment for malignancy. In an additional study by another laboratory of 55 nonreportable NIPT results⁵, the same type of “saw tooth” pattern was observed in the genome-wide representation of DNA gains and losses. Clinical follow-up information was available on 43 women; 40 of them had a confirmed neoplasm (18 malignant, 20 “benign” uterine fibroids, and two with radiological, but not pathological confirmation).⁵ In preparation for the debate, one of the authors (DWB) reviewed the cases of incidental maternal malignancies published or presented orally at scientific meetings to date and came up with 16 cases of lymphomas (43%), five cases of leukemias, six cases of breast cancers, four of colorectal cancers, two leiomyosarcomas, two of multiple myeloma, and five miscellaneous (1 case each). Cases that were known to be reported in more than one publication were only considered once.

Given the increasing numbers of women who have been determined to have cancer following unusual NIPT results, there is concern on the part of health care providers as to whether the results should be disclosed and how they should influence further management. A survey of over 300 genetic counselors in the United States¹⁰ demonstrated that 77% would disclose NIPT results suggestive of malignancy, but over half were uncomfortable providing post-test counseling. Most genetic counselors (91%) felt that institutional or national guidelines were needed for clinical management.

In a recent commentary, Carlson and colleagues created an algorithm to guide post-test evaluation of pregnant women suspected of having cancer due to the detection of more than one aneuploidy via NIPT.¹¹ Their recommendations included discussing the test results with

the clinical laboratory and performing a complete history and physical examination on the patient. Additional testing that was recommended included: a complete blood count with peripheral smear, a metabolic panel, fecal occult blood and Pap tests, a chest radiograph and an MRI of the chest, abdomen and pelvis. This commentary did not specifically indicate when a consultation with an oncologist should be obtained. Many oncologists are unaware of the fact that cancers are being detected during pregnancy through prenatal screening for fetal aneuploidy. Note that in a different study by Snyder *et al.*, only seven of 39 women (18%) whose NIPT results showed multiple aneuploidies had cancer.¹² Therefore, if these recommendations are followed, there will be women who will have a negative work-up. Similarly, of the 10 cases of cancer in this study, three did not present with multiple aneuploidies.¹² Limiting the work-up to women with a result of multiple aneuploidies will miss some of the true cases of maternal malignancy.

Another approach is taken in Belgium, where incidental NIPT findings are routinely disclosed, oncologists are routinely consulted and whole-body MRIs are regularly obtained if the profiles across the genome shows multiple areas of duplication and deletions.¹³ In one study, three cases of malignancy were diagnosed pre-symptomatically by MRI.¹⁴

Thus, in some places in the world NIPT results suggestive of cancer are disclosed and influence post-test management, and in others they are not reported. Significant variation in clinical practice is an excellent reason to have a debate!

Please note that at the initial voting, before the debaters made their respective arguments, a majority of the audience voted in favor of disclosing the incidental results.

For

(Sharon E. Plon, Debater)

I will argue for the disclosure of potential maternal cancer findings from non-invasive prenatal testing (NIPT) results for three distinct reasons. The first argument considers the lack of alternative methods of cancer screening or diagnosis available for women of child-bearing age. Currently, there is almost no routine, population-based cancer screening in the typical age range of pregnant women other than for cervical cancer. The age of starting screening mammograms and colonoscopies differs by country, but generally does not begin until age 40. However, it is estimated that 1 in 1000 pregnant women will be diagnosed with cancer.³ While cancer in pregnancy is rare, it does occur and these malignant neoplasms require treatment. Thus, if abnormal NIPT results suggestive of malignancy are not returned, cancer diagnosis maybe delayed until the patient is symptomatic. I would categorize this problem under the concept of “harmful secrets”. This term was used to describe the general problem that occurs when medically actionable genetic results are not returned from genomic sequencing tests (see third point I below).¹⁵

As a concrete example of the potential harm of not disclosing these types of NIPT results, I want to return to the first patient described by Dr. Bianchi.^{6,7} In preparation for the debate, I had the opportunity to interview Erin Lindquist, PhD (who gave permission for her name to be used) in May 2018. As already described, Dr. Lindquist’s NIPT results were unusual with

multiple chromosomal aneuploidies (confirmed by two different testing laboratories). A diagnostic procedure (amniocentesis) showed that her son had a normal karyotype. He was born healthy and the NIPT results were attributed at the time to confined placental mosaicism. There was no mention to her or her physicians that this might represent maternal cancer, although Dr. Lindquist remembers thinking about this possibility. Early in her pregnancy she was very healthy and athletic. However, towards the end of her pregnancy she started to have chronic and unexplained abdominal pain with increasing need for bedrest, and eventually she had a pathologic fracture prior to her cancer diagnosis. Dr. Lindquist strongly argued that the fact that her doctors were unaware that the NIPT result might indicate maternal cancer was harmful to her well-being. This is in sharp contrast to a prior commentary arguing that there was no benefit to potentially diagnosing her earlier.¹⁶ Similarly, many of my patients and their families describe months of unexplained symptoms, lost work, worry and unnecessary diagnostic tests focusing on more common disorders prior to a cancer being diagnosed. Thus, waiting until cancer is diagnosed through another method is not without potential harm to the patient.

Second, for many of the cancer types reported to date, earlier stage at diagnosis may reduce intensity of treatment and is associated with improved survival.¹⁷ In particular, early diagnosis of colorectal malignancy significantly improves survival and limits the need for potentially toxic treatments.¹⁸ For breast cancer, lymphoma and leiomyosarcoma, the size and extent of the tumor may alter the success rates of complete surgical resection and potentially changes the type of additional chemotherapy and/or radiation therapy that is recommended. For those women diagnosed with leukemia or myeloma it is less likely that the timing of diagnosis will alter treatment decisions. However, these latter two malignancies often result in non-specific symptoms (e.g., fevers, infection) that would most likely be confused with other non-malignant disorders. A cancer diagnosis in 7 of 49 cases with multiple aneuploidies is much higher than the vast majority of cancer screening tests currently in use.⁵ As opposed to Dr. Bianchi's description, I would argue that these data strongly argue that for NIPT results with multiple aneuploidies (1 in 10,000 NIPT cases), the test report should note that it is suggestive of concurrent maternal malignancy and provide the pregnant woman and her physician an estimate of the detection rate and the possibility of a false positive result.

My third argument for disclosing NIPT results suggestive of potential maternal malignancy is simply that women are likely to want these results and this is consistent with supporting the ethical principle of autonomy. To my knowledge, there has not been any substantial study of this specific question. However, with the explosion in genome-scale testing (in both research and clinical settings) there have been many different studies asking adult patients, parents of pediatric patients, and clinicians about their interests in receiving or disclosing a wide variety of genetic results. I focus here on two meta-analyses that were done specifically about incidental or secondary findings in the setting of clinical testing consistent with an unexpected maternal malignancy NIPT result. In 2012, when exome and genome sequencing were just becoming available, a meta-analysis combining results from four studies (2660 individuals) generated a list of themes what were important to patients and physicians having clinical genome-scale testing.¹⁵ These included respecting patient autonomy and patient welfare, recognition of a moral and/or legal obligation to disclose, as well as the

potential for results to be harmful. In particular, the concept of harmful secrets was raised by the authors and many participants expressed discomfort with the idea of secrets about their health being kept from them and healthcare professionals were wary that secrets can be destructive or harmful. A meta-analysis of many more studies was performed in 2016 that included 11,516 stakeholders.¹⁹ Overall 95–100% of patients or clinicians queried reported a high desire to receive or return, respectively, genetic findings that are potentially clinically actionable. In multiple studies, over 50% wanted results even if they weren't actionable. Our own work interviewing pediatric oncologists and parents of childhood cancer patients prior to exome sequencing also revealed that physicians over-predict the potential harm to parents in receiving genomic information, including unexpected or incidental findings.²⁰ Thus, a decision to not return NIPT results suggestive of maternal malignancy would be in stark contrast to a growing body of consistent research results that suggest that patients want to receive these types of genomic results and clinicians do not want to withhold them.

In summary, my recommendation is to prevent the development of harmful secrets! Although not within the scope of this brief debate summary, some authors have published recommendations for the appropriate work-up¹¹ for the small number of women with NIPT results such as multiple aneuploidies suggestive of the possibility of maternal cancer. In the last two years many of the same testing laboratories offering NIPT are now offering circulating tumor DNA tests as there is substantial overlap in the two test methodologies.²¹ Thus, prior concerns about the lack of familiarity with circulating tumor DNA patterns by NIPT labs are diminishing. These liquid biopsy tests could aid in follow-up of unusual NIPT results including facilitating the identification of the specific type of underlying malignancy in the patient. Other diagnostic modalities, such as whole-body MRI, are also becoming increasing available for evaluation of suspected malignancy similar to studies performed in patients with hereditary cancer predisposition syndromes²². Clearly, professional organizations such as the International Society for Prenatal Diagnosis should partner with cancer and pathology organizations to develop guidelines for consistent downstream testing after abnormal NIPT results, including defining which types of results should trigger the downstream investigations and the likelihood of detecting a malignancy.

Against

(Peter Benn, Debater)

For most practitioners in prenatal diagnosis, NIPT has a defined purpose; it is screen for *fetal* trisomies 21, 18, and 13. It may also include sex chromosome abnormalities and some microdeletion syndromes. Like any other screening test, NIPT should not include findings of unknown significance (no positive predictive value (PPV), no clear management plan, no phenotype available), or aspects of the testing for which there was no prior patient consent. If we are to consider all findings that are inconsistent with a viable fetus but potentially indicative of maternal malignancy (e.g. full autosomal monosomy or highly complex abnormal karyotype), we fundamentally alter the purpose of the test. We conflate the screening for constitutional abnormalities in the fetus with maternal cancer screening.

When NIPT is constrained to only those disorders that are compatible with fetal chromosome imbalance (as defined above), the possibility of a false-positive due to maternal cancer is exceedingly low; perhaps less than 1 in 1,800 positive cases.⁹ This risk is less than the 1 in 1,000 overall rate of cancer diagnosis during pregnancy.³ False-positives due to maternal cancer are therefore not a major concern.

When we now consider the additional chromosome abnormalities compatible with cancer, the available evidence indicates that cf-DNA analysis has a low detection rate (DR) and a relatively high false-positive rate (FPR). Based on the 1 in 1,000 pregnancy cancer rate, cell-free DNA results suggestive of monosomy 13, 18, 21 or complex abnormal combinations of these chromosomes would have a DR of about 6%.^{9,12} Approximately 1 in 1,000 women will be falsely alarmed about a risk for cancer. This is almost as high as the FPR for fetal trisomy 13, 18 and 21 combined (1 in 833).²³ The PPV for maternal cancer would be approximately 6%.

Some laboratories have chosen to extend NIPT to look at all large imbalances and these laboratories can be expected to identify additional cases of maternal malignancy.^{5,9,14} However, the false-positive rate is higher. Based on cytogenetic studies of cytotrophoblasts (the same lineage as “fetal” cf-DNA), perhaps an additional 0.8% of cases will show a positive result, mostly attributable to a rare autosomal mosaic trisomy confined to the placenta.²⁴ Unless the findings are confirmed through chorionic villus biopsy with cytotrophoblast analysis, many of these women would also need to be considered at increased risk for malignancy because these imbalances could also be compatible with cancer.

This burden of false-positives constitutes only one aspect of the problems associated with conflating fetal and maternal malignancy screening. Because an individual woman’s risk for maternal cancer can be appreciable, the possibility needs to be disclosed prior to testing.²⁵ Pre-test counseling is already highly complex and it unclear how this additional information could be integrated. How do we manage the patient who opts-in for fetal abnormalities but opts-out for maternal cancer screening (or vice versa)? A patient who is morally opposed to any type of pregnancy intervention and would not consider prenatal testing is placed in an ethical dilemma when she is told the test is also used to assess her health. How do we incorporate prior risk factors (maternal age, smoking, family history, etc.) in determining the cancer risk? Should we change the gestational age of the test if a patient’s primary concern is cancer? Indeed, if we are to accept that there truly is benefit in providing cf-DNA screening for cancer, why not offer the test to all non-pregnant individuals?

Management of patients with positive results is also highly problematic because the tumor type is not defined. As stated earlier, a step-wise work-up has been proposed,¹¹ but it is highly burdensome, stressful and expensive. This suggested work-up did not mention exclusion of fibroids,⁵ auto-immune disease²⁶ or stress the need for invasive prenatal testing at least in some cases. How many true-positive women will elect to be treated immediately and how many will wait until after delivery? What are the consequences of cancer therapies on the fetus? The benefit of early diagnosis and treatment is clear for some types of cancer, but there are also situations where treatment can be delayed.¹⁶ How many women with

unexplained positive tests will terminate their pregnancy fearing that they will not be able to care for their baby? What is the impact of a positive test on maternal/fetal bonding?²⁷ To what extent does the stress associated with a positive result lead to preterm birth, low birth weight, or serious psychological harm at a time when women are particularly vulnerable?²⁸

There are lessons from other laboratory tests that are associated with cancer.²⁹ Maternal serum alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG) are routinely measured in pregnancy. Although these markers are considered helpful in evaluating patients with hepatocellular carcinoma and germ cell tumors, these tests are not used for routine cancer screening. Pregnancy is a confounder when using AFP and hCG for cancer monitoring. Other serum markers such as CA-125 and CEA have value in monitoring cancers but are not recommended for routine population screening. This is because a net clinical benefit cannot be demonstrated. Where is the evidence that cf-DNA is a better biomarker?

To purposefully consider the additional chromosome abnormalities typically seen in cancers generally requires a screening program policy decision. This should not be confused with diagnostic test “incidental findings” which are unintentional. Highly publicized cases where cancer was identified through NIPT have emotional appeal, but this does not alter the need for objective evaluation of benefit versus harm that should precede a policy decision to always disclose.

It has been argued that there are NIPT cases where the evidence for maternal disease is compelling and disclosure is necessary. These are exceptional and far removed from always disclosing.

We need to optimize cf-DNA testing for specific cancers, conduct the appropriate clinical trials, determine the correct population and time to offer testing. In the meantime, we should recognize that cf-DNA testing has not been optimized or validated as a screening test for cancer during pregnancy.

Summary

In essence, the debate crystalized around the potential health benefits of early cancer detection versus the potential anxiety that would be generated at a particularly vulnerable time during pregnancy. Dr. Plon drew upon her clinical experience in a cancer genomics clinic and emphasized the importance of not keeping “harmful secrets” from individuals. In contrast, Dr. Benn drew upon his experience as a clinical genetics laboratory director, focusing on his concerns regarding the release of a test that has not been designed or validated for cancer screening. After some audience questions, voting was repeated, and the majority of the audience once again voted in favor of disclosing incidental NIPT results that suggest maternal cancer.

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