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Noninvasive Prenatal Test Results Indicative of Maternal Malignancies: A Nationwide Genetic and Clinical Follow-Up Study

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abstract

PURPOSE Noninvasive prenatal testing (NIPT) for fetal aneuploidy screening using cell-free DNA derived from maternal plasma can incidentally raise suspicion for cancer. Diagnostic routing after malignancy suspicious–NIPT faces many challenges. Here, we detail malignancy suspicious–NIPT cases, and describe the clinical characteristics, chromosomal aberrations, and diagnostic routing of the patients with a confirmed malignancy. Clinical lessons can be learned from our experience.

METHODS Patients with NIPT results indicative of a malignancy referred for tumor screening between April 2017 and April 2020 were retrospectively included from a Dutch nationwide NIPT implementation study, TRIDENT-2. NIPT profiles from patients with confirmed malignancies were reviewed, and the pattern of chromosomal aberrations related to tumor type was analyzed. We evaluated the diagnostic contribution of clinical and genetic examinations.

RESULTS Malignancy suspicious–NIPT results were reported in 0.03% after genome-wide NIPT, and malignancies confirmed in 16 patients (16/48, 33.3%). Multiple chromosomal aberrations were seen in 23 of 48 patients with genome-wide NIPT, and a malignancy was confirmed in 16 patients (16/23, 69.6%). After targeted NIPT, 0.005% malignancy suspicious–NIPT results were reported, in 2/3 patients a malignancy was confirmed. Different tumor types and stages were diagnosed, predominantly hematologic malignancies (12/18). NIPT data showed recurrent gains and losses in primary mediastinal B-cell lymphomas and classic Hodgkin lymphomas. Magnetic resonance imaging and computed tomography were most informative in diagnosing the malignancy.

CONCLUSION In 231,896 pregnant women, a low percentage (0.02%) of NIPT results were assessed as indicative of a maternal malignancy. However, when multiple chromosomal aberrations were found, the risk of a confirmed malignancy was considerably high. Referral for extensive oncologic examination is recommended, and may be guided by tumor-specific hallmarks in the NIPT profile.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Noninvasive prenatal testing (NIPT) has been implemented worldwide as a screening test for fetal aneuploidy. NIPT can be based on shallow whole-genome sequencing of cell-free DNA (cfDNA) derived from maternal blood, which contains both maternal and placental cfDNA, the latter being representative of fetal DNA. Intrinsic to screening tests, discordant results between NIPT and fetal genotype may sometimes occur. Causes of discordant-positive NIPT results are, among others, confined placental mosaicism and (occult) maternal malignancies.[1-3] When cfDNA of apoptotic or necrotic tumor cells is shed into the maternal bloodstream, aneuploidies of these tumor cells may be detected by NIPT. In particular, multiple chromosomal aberrations are indicative of a maternal malignancy. As NIPT uptake increases, especially those reporting genome-wide analysis, more potential cases of malignancy will be referred to oncology. These cases have unique diagnostic challenges: pregnancy-related symptoms may mask an underlying malignancy, patients could be asymptomatic, and the pregnancy must be taken into account in choosing examinations.

We report real-life management of cases in which NIPT results were assessed as indicative of maternal

CONTEXT

Key Objective

Maternal malignancies are incidentally discovered by noninvasive prenatal testing (NIPT). We assessed the NIPT profiles that were suspicious for cancer in a national screening program. We evaluated the genomic alterations, the clinical workup, and detected tumor types to create and tailor recommendations for future clinical care.

Knowledge Generated

Genome-wide analyses identified more cases with malignancy suspicious–NIPT than targeted NIPT. When restricting the analyses of an abnormal genome-wide NIPT to cases with >1 chromosomal aberration, a malignancy was confirmed in about 70% of cases. We found recurrent chromosomal gains and losses in primary mediastinal B-cell lymphoma and classic Hodgkin lymphoma.

Relevance

Although a malignancy suspicious–NIPT is rare, the high incidence of a confirmed malignancy following a malignancy suspicious–NIPT can be directly used in clinical practice, enabling malignancy-focused counseling and prompting an efficient diagnostic workup that may be guided by tumor-specific hallmarks in the NIPT profile.

malignancies. Our study population was derived from the TRIDENT-2 study, a nationwide, first-tier NIPT implementation study for all pregnant women in the Netherlands.[4] By analyzing the clinical tumor characteristics, genomic landscape of chromosomal aberrations, and diagnostic routing, we aim to determine whether certain NIPT results could be addressed to a maternal malignancy, so future NIPT reporting could be improved. Furthermore, we aim to create and tailor recommendations for future clinical care of women with a suspected malignancy on the basis of NIPT.

METHODS

Study Oversight and Population

This retrospective study included pregnant women with chromosomal aberrations indicative of a maternal malignancy detected by NIPT (hereafter, malignancy suspicious–NIPT), and referred to a clinical geneticist, medical oncologist, and/or hematologist, as part of the TRIDENT-2 study between April 2017 and April 2020. The eligibility criteria, implementation data, and preliminary case data from the first year of the TRIDENT-2 study have been reported before.[4,5] Women with a known malignancy at the time of NIPT were excluded from TRIDENT-2. Participants could choose between receiving NIPT results for chromosomes 13, 18, and 21 only (targeted NIPT), or for all autosomes (genome-wide NIPT). Sex chromosomes were not analyzed. The initial decision for a malignancy suspicious–NIPT result was documented in the NIPT report by clinical laboratory geneticists working at one of three Dutch academic NIPT laboratories, using comparable report language (Data Supplement, online only). Criteria were established in national consensus meetings and on the basis of international literature data.[6-9] All women who received a malignancy suspicious–NIPT result were referred to a clinical geneticist at one of eight academic hospitals. These women were offered invasive prenatal testing (either amniocentesis or chorionic villus sampling) and molecular, genetic, and/or cytogenetic analysis of blood lymphocytes to exclude a fetal or constitutional maternal origin of the chromosomal aberrations, respectively. Furthermore, the patients were referred to a medical oncologist and/or hematologist for further diagnostic testing and clinical care. The type of examination(s) was at the physician's discretion. If no clinical explanation for the abnormal NIPT result was established, in general the women were offered a postpartum NIPT and/or genetic testing of placenta biopsies.

License and Ethical Approval

A license for the TRIDENT-2 study was granted by the Minister of Health, Welfare, and Sport (1017420-153371-PG) to all eight University Medical Centers. The study was approved by the Medical Ethics Committee of VUMC Amsterdam (No. 2017.165). Written informed consent from all women was obtained, including the collection and use of medical follow-up data from health care providers for scientific research.

Recruitment and Data Collection

We collected malignancy suspicious–NIPT data from the three Dutch NIPT laboratories, and genome diagnostic data from all eight Dutch academic departments of clinical genetics, as well as clinical follow-up data from the treating physicians or general practitioner. Patients with more than one NIPT, because of subsequent pregnancies ($n = 2$), were considered as one case. If a maternal malignancy was confirmed, we contacted the treating oncologist or hematologist to request additional information on tumor type and stage, examinations performed, and if applicable, on the initial oncologic treatment. Follow-up information was collected until January 2021.

NIPT, Data Analysis, and Visualization

Sample processing, sequencing, and downstream bioinformatical analyses were performed as previously described (Data Supplement).[4] In brief, all maternal peripheral blood samples were collected at or after a gestational age of 11 weeks, and cfDNA was isolated from plasma and subjected to shallow whole-genome sequencing and WISECONDOR analysis (v2.0.1) at standard settings.[10] For this study, all malignancy suspicious–NIPT profiles were individually reviewed to ensure the chromosomal aberrations were uniformly displayed. Only copy-number variants (CNVs) ≥ 10 megabase or CNVs crucial in clinical decision making, on the basis of literature and/or genetic resources, were documented. For visualization of genomic data, Progenetix bioinformatic freeware program was used.[11,12]

RESULTS

From April 2017 to April 2020, a total of 231,896 NIPT assays were performed in the TRIDENT-2 study (Fig 1). In 27.0% (63,444), aneuploidy analysis of chromosomes 13, 18, and 21 only was requested (targeted NIPT) and in 73.0% (168,452), analysis of all autosomes was requested (genome-wide NIPT). A malignancy suspicious–NIPT was reported in 53 cases (0.02%). Of 53 malignancy suspicious–NIPT results, 50 (94.3%) were reported after genome-wide NIPT and three (5.7%) after targeted NIPT. This resulted in 0.03% (50/168,452) malignancy suspicious–NIPT reports in the genome-wide group and 0.005% (3/63,444) in the targeted group. Of the 50 patients in the genome-wide NIPT group, two appeared to be diagnosed with a myeloproliferative neoplasm before pregnancy and were therefore excluded from further

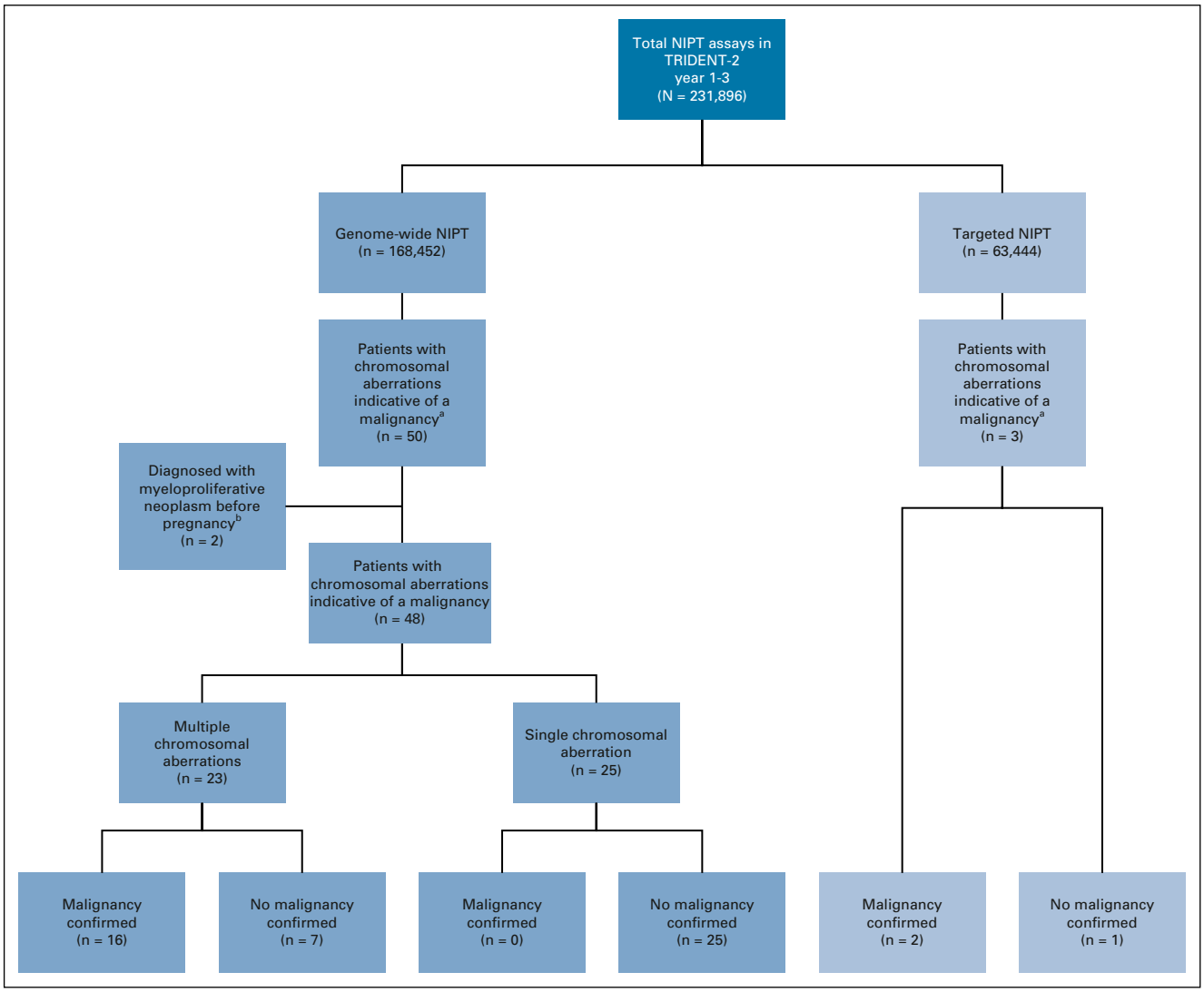

FIG 1. Flow diagram of the study population. The figure shows the total number of NIPT assays in the first 3 years of the TRIDENT-2 study, and the patients in the different (sub)groups. [a]All patients in whom the initial NIPT result was assessed as a malignancy suspicious–NIPT. [b]Two patients were excluded because they were diagnosed with a myeloproliferative neoplasm before pregnancy. This was not known by the clinical laboratory geneticist at the time of the initial assessment of the NIPT result. NIPT, noninvasive prenatal testing.

analyses. A malignancy was confirmed in 18 patients, 16/48 (33.3%) patients in the genome-wide group and 2/3 patients in the targeted group. In the remaining 33 patients, no malignancy was found. Of the 48 patients with a genome-wide NIPT, 23 showed multiple (≥ 2) chromosomal aberrations and a malignancy was confirmed in 16 of these (16/23, 69.6%). In the 25 patients with a single aberration in genome-wide NIPT, no malignancies were found. For the three patients who requested a targeted NIPT, single or multiple aberrations could not be distinguished because the presence of additional aberrations on other chromosomes cannot be excluded. The median maternal age at NIPT sampling for the 18 patients with a confirmed malignancy was 35 years (range, 26-42 years), and 33 years (range, 26-41 years) for patients without a malignancy.

Patients With a Confirmed Malignancy

Clinical and pathologic characteristics. The 18 patients diagnosed with a malignancy presented with different tumor types and different tumor stages (Fig 2). All malignancies were pathologically confirmed. Most of the malignancies were of hematologic origin (n = 12, 66.7%). Hodgkin lymphomas (n = 7) were all classified as classic Hodgkin lymphomas (cHLs), and non-Hodgkin lymphomas (n = 4) were all classified as primary mediastinal B-cell lymphomas (PMBCLs). Breast cancers (BrCs; n = 4) were triple-negative (n = 2), estrogen receptor/progesterone receptor–positive/human epidermal growth factor receptor 2 (HER2)–negative (n = 1), and estrogen receptor/progesterone receptor–negative/HER2-positive (n = 1). Acute myeloid leukemia (AML), colorectal carcinoma, and a carcinoma of unknown primary were diagnosed in one patient each.

Chromosomal aberrations found with NIPT. Figure 3A shows the different CNVs found with NIPT for each individual patient diagnosed with a malignancy. A detailed description of the CNVs, including the corresponding cytogenetic bands,[13] is shown in the Data Supplement. Case C12 shows a specific gain of *HER2* at chromosome band 17q21. Despite its size (< 10 megabase), this finding was crucial for raising suspicion of BrC, and amplification of *HER2* was confirmed. Figure 3B shows the genomic landscape of NIPT results grouped across the most frequent tumor types found. Recurrent CNVs in cHL were (partial) gains of 2p (5/7, 71.4%), 5p (4/7, 57.1%), and 9p (3/7, 42.9%), and (partial) losses of 11q (4/7, 57.1%), and 6q, 7q (3/7, 42.9%). For PMBCL, a recurrent (partial) gain was seen on 9p and 9q (3/4, 75.0%), 2q, 8q, 12q, and 18q (2/4, 50.0%), and a recurrent (partial) loss of 16q (2/4, 50.0%). The Data Supplement shows the genomic localizations of key genes in relation to the cumulative CNVs in all malignancies. Interestingly, case C4, which had two NIPT results with a 15-month interval, showed additional CNVs in the second sample (Data Supplement). This cHL case was not diagnosed at clinical evaluation after the first malignancy suspicious–NIPT, but following additional examinations after the second NIPT.

Diagnostic routing. Figure 4 provides an overview of the various examinations performed for the patients diagnosed with a malignancy. In case C14, diagnostic testing was not

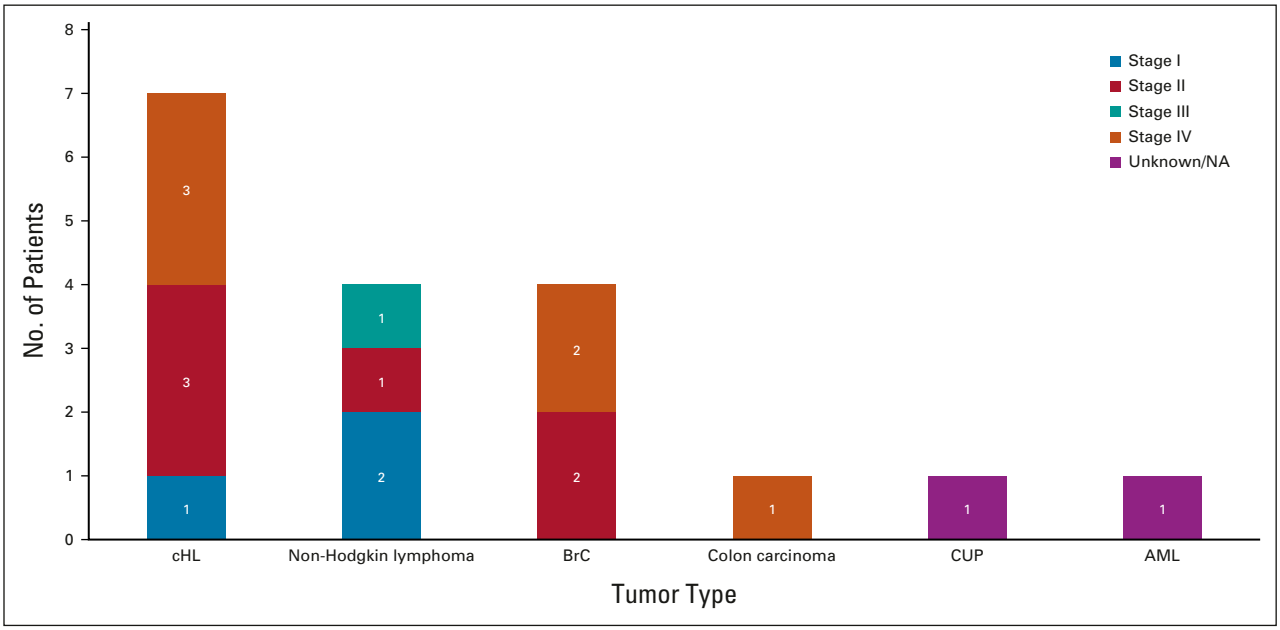

FIG 2. Tumor types and stage at diagnosis. Different tumor types as well as the corresponding stages at initial diagnosis are shown. The numbers on the *y*-axis represent the number of patients. AML, acute myeloid leukemia; BrC, breast cancer; cHL, classic Hodgkin lymphoma; CUP, carcinoma of unknown primary; NA, not applicable.

FIG 3. Genomic landscape of cfDNA detected CNVs of ≥ 10 megabase with NIPT in the patients with a confirmed malignancy. (A) cfDNA detected CNVs with NIPT per individual patient. Cases are ordered by unsupervised hierarchical clustering. The two targeted NIPT assays are shown at the bottom. In the figure, each horizontal line represents a unique patient, followed by the abbreviation of the tumor type. Vertical purple lines in the depicted chromosomes represent the position of the centromeres. Only autosomes are included in the figure. Chromosome 19 analysis by WISECONDOR is less reliable, because of shortage of reference bins, but displayed for completeness. Gains are shown in yellow and losses in blue. Individual distinct calls located in close proximity of each other may be displayed as single instead of multiple genomic events. For details of the CNVs, see the Data Supplement. [a]Targeted NIPT. (B) cfDNA detected CNVs with NIPT grouped across the most frequent tumor types found. Upper panel: the percentage on the *y*-axis indicates the percentage of the tumors with the respective chromosomal aberration. Vertical purple lines in the depicted chromosomes represent position of the centromeres. Only autosomes are included in the figure. Lower panel: heatmap showing merged profile of chromosomal aberrations in each tumor entity. Gains are shown in yellow and losses in blue. Black indicates no copy-number aberration. The brightness of the colors correlates with the frequency of the aberrations, with brighter colors indicating a higher frequency. Numbers of patients with tumors in each category are shown between brackets. Individual distinct calls located in close proximity to each other may be displayed as single instead of multiple genomic events. In one of the BrC cases, a targeted NIPT was performed. AML, acute myeloid leukemia; BrC, breast cancer; cfDNA, cell-free DNA; cHL, classic Hodgkin lymphoma; CNV, copy-number variant; CRC, colorectal cancer; CUP, carcinoma of unknown primary; NIPT, noninvasive prenatal testing; PMBCL, primary mediastinal B-cell lymphoma.

described as the malignancy was diagnosed between NIPT sampling and the NIPT result. Physical examination was reported abnormal in 4/17 (23.5%) patients: enlarged lymph nodes (C2(2), C6, C8) were found in three cases, and a breast lesion was detected in one case (C13). In one patient (C18), the hematologic blood test was indicative of AML. In all five patients who underwent a total body magnetic resonance imaging (MRI), a malignancy was revealed. If an abdominal MRI was performed, combined with a thorax and neck computed tomography, at least one of these modalities indicated the presence of a malignancy. Invasive prenatal testing was performed in 10 patients, all with normal results (Data Supplement). In addition, (molecular) cytogenetic examination of maternal leukocytes provided an explanation for the chromosomal aberrations found with NIPT in only one patient (C18).

Time of diagnosis, treatment, and follow-up. The median time between NIPT result and diagnosis of cancer was five weeks with a maximum of 81 weeks. In 15 patients, the

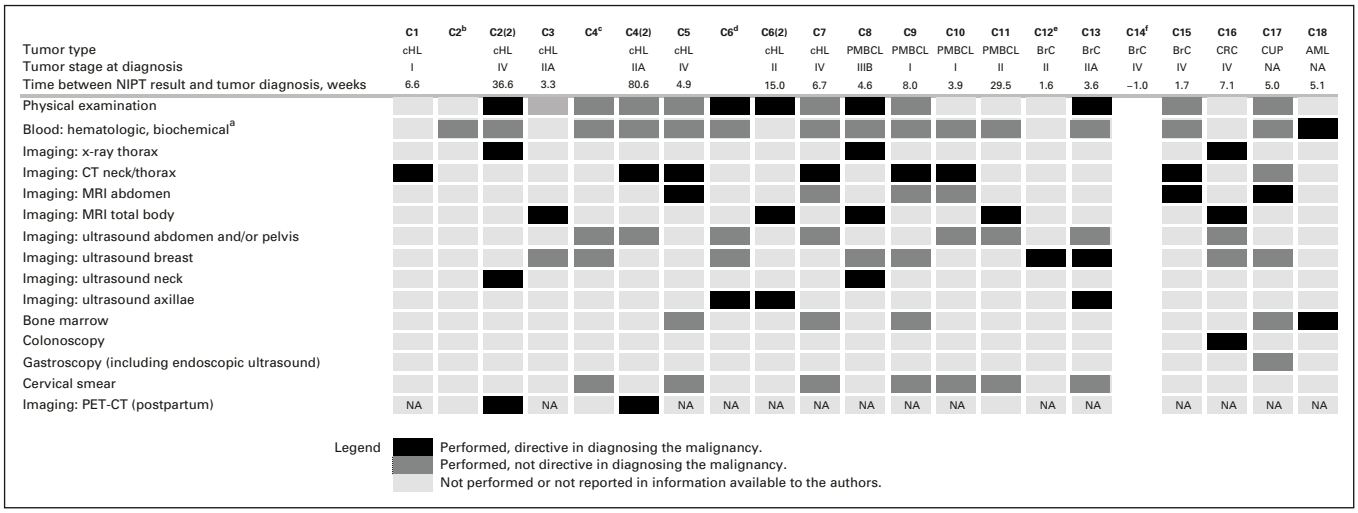

FIG 4. Overview of diagnostic examinations performed by the hematologists and/or medical oncologists in patients with a confirmed maternal malignancy. The upper part gives information per individual patient about tumor type, tumor stage at diagnosis, and time between NIPT result and tumor diagnosis; for the latter, the pathologic diagnosis was leading. In this heatmap, each row includes a different diagnostic modality, and each column represents a patient with the exception of three columns that show the examinations performed in the same patient in a later period, indicated as (2). The heatmap only includes examinations that were performed to diagnose or stage the malignancy, as reported by the treating physician. Examinations performed later to evaluate treatment or disease are not shown. [a]The results from hematologic and clinical biochemical blood tests were abnormal in three patients and probably suggestive of an underlying malignancy; however, the findings were unspecific and not directive in diagnosing the malignancy. This involved one case with an elevation of the erythrocyte sedimentation rate (C5), and two cases of elevation of the level of lactate dehydrogenase LDH (C8, C2(2)). [b]C2: no malignancy was diagnosed on the basis of the examinations performed directly after the NIPT result. C2(2) examinations performed 8 months after the NIPT result on the basis of symptoms. [c]After these examinations, NIPT was not repeated per patient's request. NIPT postpartum was also offered but the patient refused; several months later, the patient contacted physician to repeat the NIPT and subsequently more examinations were performed to diagnose the malignancy (C4(2)). [d]C6: no malignancy could be confirmed after the first examinations; C6(2) tests were repeated several weeks later, and the malignancy was confirmed. [e]On the basis of the patient's request, only ultrasound of breasts was performed. In addition, a specific gain of chromosome region 17q12 (*ERBB2* gene) was found in NIPT. [f]Malignancy was diagnosed just before the NIPT result; therefore, the examinations performed to diagnose the malignancy were not based on the NIPT result. AML, acute myeloid leukemia; BrC, breast cancer; cHL, classic Hodgkin lymphoma; CRC, colorectal cancer; CT, computed tomography; CUP, carcinoma of unknown primary; MRI, magnetic resonance imaging; NA, not applicable; NIPT, noninvasive prenatal testing; PET, positron emission tomography; PMBCL, primary mediastinal B-cell lymphoma.

malignancy was diagnosed during pregnancy, and in three postpartum. Chemotherapy was administered to 10/15 patients during pregnancy. Of the remaining five patients, two patients terminated their pregnancy because of poor maternal prognosis and subsequently started with systemic treatment, two patients postponed treatment and labor was initiated at a gestational age between 32-35 weeks, and one patient initially refused treatment. The intention of treatment was curative in 13 patients and palliative in five patients (Data Supplement). Of the 16 ongoing pregnancies, 15/16 (94.0%) resulted in a live birth with a median gestational age of 38^{+3} weeks (range, 33^{+1} to 42^{+1} weeks), and one resulted in a stillbirth at a gestational age of 31^{+1} weeks (Data Supplement).

Patients in Whom No Maternal Malignancy Was Found

In 33/51 (64.7%) patients, no malignancy was found after tumor screening, and 32/33 of these women had chosen a genome-wide NIPT. Of the 32 genome-wide NIPT results, seven showed multiple chromosomal aberrations, and 25 a single CNV gain or loss. The single CNVs consisted in particular of deletions of chromosome 5q (n = 6) or 20q (n = 11), regions known to be associated with hematologic malignancies. Details of the CNVs are shown in the Data Supplement. The diagnostic examinations and tests performed differed in individual patients depending on the NIPT result, ranging from blood tests only to total body MRI. In 26/33 patients a nonmalignant maternal, fetal, or placental condition was identified and clinically interpreted as possibly related to the chromosomal aberrations established with NIPT, and in seven patients, this remained unknown (Table 1).

DISCUSSION

We describe the real-life management of reported NIPT cases indicative of a maternal malignancy in pregnant women not known to have a malignancy at the time of inclusion in the nationwide TRIDENT-2 study. The TRIDENT-2 study is an NIPT implementation study that screens for fetal aneuploidy using cfDNA derived from maternal blood. Unique to earlier reports, we present data of a multicenter clinical follow-up of 18 malignancy cases, together with the detailed description of genomic aberrations that were identified using targeted and genome-wide NIPT.[1-3,14-16] Of the 231,896 performed

TABLE 1. Patients in Whom No Malignancy Was Found

Other Condition Identified (n = 26)[a]	No. of Patients
Genome-wide NIPT (n = 25)	
Multiple aberrations (n = 6)	
Maternal	
Uterine myomas	2
Cell lysis (congenital hemolysis, familial Mediterranean fever)	2
Placental	
Chromosomal aberrations partially detected in placental biopsies	1
Fetal	
Decreasing signal of chromosomal aberrations over time in the NIPT, possible vanishing twin	1
Single aberration (n = 19)	
Maternal	
(Mosaic) constitutional and/or somatic CNVs[b]	16
Previously diagnosed with paroxysmal nocturnal hemoglobinuria	1
Placental	
Confined placental mosaicism, confirmed in placental biopsies	2
Targeted NIPT (n = 1)	
Maternal	
Uterine myomas	1

No Condition Identified (n = 7)[c]	No. of Patients
Genome-wide NIPT (n = 7)	
Multiple aberrations (n = 1)	1
Single aberration (n = 6)	6

Abbreviations: CNV, copy-number variant; NIPT, noninvasive prenatal testing.

[a]Maternal/fetal/placental conditions identified in patients in whom no malignancy was found, and clinically interpreted as possibly related to the chromosomal aberrations established with NIPT (n = 26).

[b]Clinical conclusions were based on genetic examinations performed on maternal lymphocytes, hair roots, saliva, and/or bone marrow. Per patient, different examinations were performed. For details of the CNVs, see the Data Supplement.

[c]Unknown explanation for the chromosomal aberrations established with NIPT (n = 7).

NIPT assays, 0.03% of women in the genome-wide group and 0.005% of women in the targeted group received an NIPT result that was assessed as indicative of a maternal malignancy. Cancer was subsequently confirmed in 18 patients, 16/48 (33.3%) patients in the genome-wide group and 2/3 patients in the targeted group. The percentage of confirmed malignancies among patients with multiple chromosomal aberrations in genome-wide NIPT was much higher, 69.6%. Various tumor types at different stages were diagnosed, with the majority being hematologic malignancies. The high risk of a confirmed maternal malignancy following a malignancy suspicious–NIPT result is important for the counseling of patients and stresses the need for an oncologic assessment. We observed an NIPT pattern of recurrent chromosomal gains and losses in the hematologic cancers PMBCL and cHL, containing key biologic factors and diagnostic targets. In PMBCL, gains were seen on chromosome 9 containing the programmed death ligand-1/programmed death ligand-2 locus and *JAK2* gene. These recurrent chromosomal aberrations in the NIPT profiles of PMBCL have also been reported in (array)–comparative genomic hybridization based studies.[17-19] The NIPT profiles of cHL patients showed gains of chromosome arms 2p, containing the *REL* gene, and 5p (Data Supplement). Identical imbalances were recently reported in studies using liquid biopsies[20,21] and microdissected or flow cytometry–sorted tumor tissue.[20] Following the observation that NIPT patterns could point to the identity of the involved malignancy, we propose to include the corresponding cytogenetic region according to the International System for Human Cytogenomic Nomenclature[13] in the NIPT report. The aberrations found with NIPT may guide further relevant clinical examinations to aid in the identification of an underlying malignancy.

In our study, we found similar tumor types as prior NIPT studies.[2,3,14,15] However, for pregnant women, in general, a different tumor spectrum is reported. Lymphoma is less prominent, but, depending on the population and cohort, BrC, cervical cancer, melanoma, and thyroid cancer are more common.[22-25] It is conceivable that hematologic malignancies are more likely to be discovered by NIPT, as these generally are liquid tumors originating in the bone marrow or in the lymphoid system, and circulating in the peripheral blood. Therefore, guidelines for diagnostic follow-up testing after a malignancy suspicious–NIPT should not be based on epidemiologic incidence rates of cancer in pregnancy, but rather the results of NIPT-based studies.

To determine whether CNVs in malignancy suspicious–NIPTs truly originate from maternal cancer, several parallel strategies can be followed, depending on the CNV pattern found. Imaging with total-body MRI, or a combination of computed tomography of neck/thorax and abdominal MRI, yielded the highest diagnostic benefit, which is in line with Lenaerts et al.[14] Moreover, because of its lack of ionizing radiation, MRI can be safely used during pregnancy.[26] Hematologic blood tests should be added in case there is a suspected hematologic malignancy. In parallel with oncologic screening, clinical genetic counseling is recommended to discuss genome diagnostics for maternal or fetal germline aberrations. Importantly, as tumor-derived CNVs may mask aberrations in fetal DNA, invasive prenatal diagnostics for the detection of fetal genetic aberrations should be offered. Especially if genome-wide NIPT shows a single chromosomal aberration, a maternal or fetal germline

origin is more likely than a malignancy.[4] In cases of targeted NIPT, it is important to be aware that (tumor-derived) CNVs involving chromosomes other than 13, 18, and 21 are not revealed. In our study, for the patients in whom no malignancy was found, the NIPT result consisted of single aberrations as well as multiple chromosomal aberrations. For the single aberrations detected in genome-wide NIPT assays, deletions 5q and 20q might indicate the presence of a maternal malignancy because of their association with AML and MDS.[27,28] However, in our study, no malignancies were confirmed in the group with deletions 5q and 20q. Clinical implications are not clear at present and need further clarification by long-term follow-up studies. In case of multiple aberrant NIPT profiles, several nonmalignant causes have been described in literature, such as uterine myomas, vitamin B12 deficiency, autoimmune disorders, and the use of heparin.[4,29,30]

The number of cases described in this study is an underestimation of the true number of malignancies occurring during pregnancy (1 in 1,000 to 2,000[31]), as NIPT is not a cancer screening test and not every malignancy can be discovered by the NIPT analysis algorithm or interpreted as such.

This study takes into account all reported malignancy suspicious–NIPT results in the Netherlands within the TRIDENT-2 study, which offered NIPT in a National Screening Program to pregnant women with an average risk for fetal aneuploidy. Therefore, the 51 malignancy suspicious–NIPT cases that were assessed for a malignancy represent real-life management. The initial assessment to report an NIPT result as suspicious of a malignancy was based on the criteria mentioned in the Data Supplement. Intrinsic to real-life management, however, the assessment by the clinical laboratory geneticist consists of a combination of these criteria, literature, and databases; therefore, small differences may have occurred in borderline cases.

With this study, we cannot answer the question whether early detection of a malignancy following NIPT translates into a better clinical outcome. However, the anxiety and uncertainty following a malignancy suspicious–NIPT requires clarity as soon as possible, and knowledge of a maternal malignancy could be of importance for decisions and planning of pregnancy management in a multidisciplinary setting. A confirmation of NIPT-detected CNVs using an independent technique or in tumor tissue was not attempted, but the recurrent CNVs detected in patients with cHL and PMBCL have been reported previously. In the future, the emerging field of cfDNA fragmentomics offers possibilities to further link cfDNA and NIPT profiles to the tissue of origin.[32,33] In addition, for future studies, it might be interesting to apply bioinformatics tools such as ichorCNA to assess a correlation between the tumor fraction in cfDNA and the copy-number changes.[34]

In conclusion, this study provides important insights into the management of a rare, but challenging group of pregnant women with a malignancy suspicious–NIPT result. The risk of a confirmed malignancy is considerably high, especially if the NIPT showed multiple chromosomal aberrations. For this group, we recommend an extensive oncologic investigation, including a total-body MRI and hematologic blood tests. The CNV pattern indicated by the NIPT may help identify the underlying tumor type, which is applicable for daily practice and counseling of these patients.

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EQUAL CONTRIBUTION

C.J.H. and S.M.A. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Noninvasive Prenatal Test Results Indicative of Maternal Malignancies: A Nationwide Genetic and Clinical Follow-Up Study

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