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CORRESPONDENCE

Noninvasive prenatal testing in CLL during pregnancy: A cautionary tale

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To the Editor:

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, with a median age at diagnosis of 72 years. An estimated 2% of the patients are females of childbearing age. CLL cases during pregnancy are rare and are associated with many complications. Although the implications and management of CLL in pregnancy have been discussed previously, issues related to noninvasive prenatal testing (NIPT) are often overlooked [1]. Various chromosomal changes are associated with CLL, with the deletion in the long arm of chromosome 13 at position q14 (deletion 13q14) being the most common alteration [2].

Since its implementation in clinical practice in 2011, NIPT was available to all pregnant women in the Netherlands in 2017. It has become a reliable and sensitive method of prenatal screening to evaluate the risk of fetal chromosomal imbalances. NIPT testing is primarily used to screen for Down (trisomy 21), Edwards (trisomy 18), or Patau (trisomy 13) syndromes. However, other deletions, such as del13q, can also be detected. NIPT can be performed as early as 10 weeks of gestations, and NIPT is based on the analysis of cell-free DNA (cfDNA) of which a small part is derived from the placenta, and the main part has a maternal origin [3]. However, with the NIPT test that is used in the Netherlands [4, 5], it is impossible to discriminate between fetal cfDNA and tumor-derived cfDNA, including CLL [6]. The finding of a chromosome aberration warrants further investigation using invasive prenatal procedures, such as chorionic villus sampling or amniocentesis. Maternal neoplasms causing aberrant NIPT results are a complex matter in prenatal diagnosis [7]. Cases describing discordant NIPT testing caused by a hematological malignancy remain very scarce [8], and this is the first report of a patient with diagnosed CLL having a discordant NIPT result post CLL diagnosis due to a molecular aberration of CLL cells.

A 33-year-old woman with a 1-year history of untreated CLL, had NIPT performed at 13 1/7 gestational weeks as a first-tier screening test for fetal aneuploidies. Ultrasound examinations at 6 and 12 gestational weeks showed a single viable intrauterine pregnancy, biometry appropriate for gestational age, and absence of gross fetal anomalies. The NIPT results indicated a high risk for chromosome 13q14 deletion (Figure 1). Genetic counseling of the woman and her partner was done. Our primary goal was to rule out the fetal origin of the abnormal result. Therefore, single nucleotide polymorphism array (SNP-array) on amniotic fluid cells and peripheral blood of the mother was performed to verify the abnormal NIPT result. While a mosaic loss of 10 Mb was identified in the maternal blood within the 13q14.11q14.3 region (arr[hg19] 13q14.11q14.3(40,484,657-50,909,942)x1~2), the amniotic fluid was normal. Fluorescent in situ hybridization (FISH) on interphase nuclei cells of the mother confirmed a mosaic deletion on 13q (Figure 2). Ultrasound scans at 16, 20, and 24 gestational weeks reported no fetal anomalies. At 40 gestational weeks labor she gave birth to a healthy male baby.

In patients with malignancies, NIPT testing can potentially lead to discordant results when the malignant cells are affected with (a) chromosome aberration(s) like in the present case. As it will complicate the accurate interpretation of the NIPT results, a maternal malignancy is a contraindication for NIPT in the Netherlands, especially when it comes to hematological neoplasms [9]. Nevertheless, the incidence

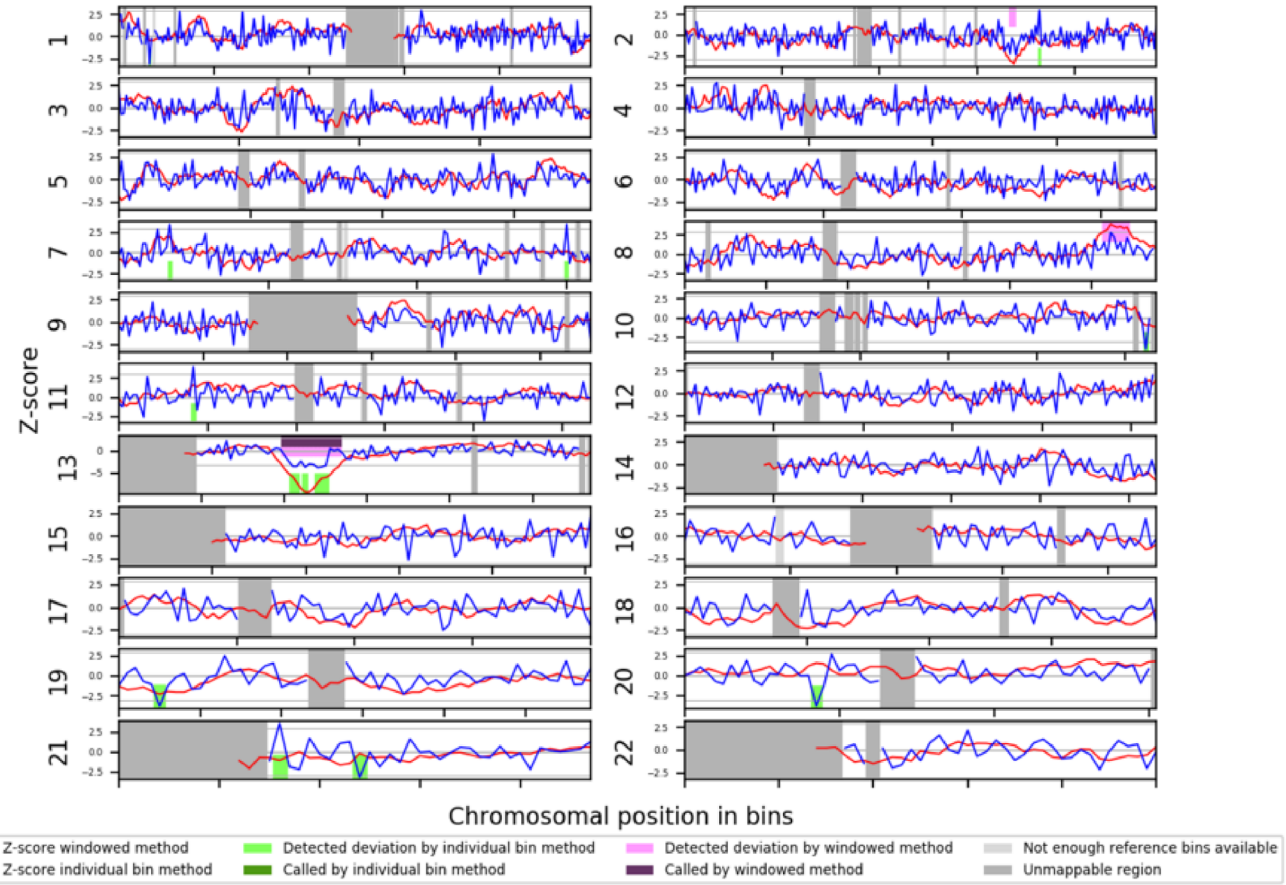

FIGURE 1 Results of noninvasive prenatal testing (NIPT) analysis with WISECONDOR [11] showing the deletion on chromosome 13q14.

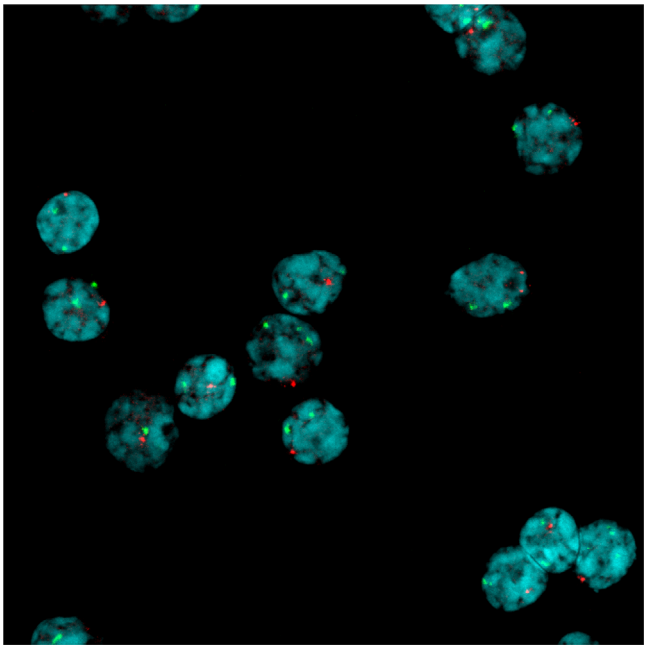

FIGURE 2 Interphase nuclei fluorescent in situ hybridization (FISH) results: Detection of 13q14.3 (D13S319, red signal) and the centromere of chromosome 12 (D12Z3, green signal), revealing a deletion of 13q14.3 (D13S319) in about 56% of cells.

of pregnancy among patients diagnosed with malignancies is notably low; therefore, it is unknown how much routine counseling by medical specialists regarding NIPT is performed in this population. The laboratory—not knowing about the CLL—interpreted the deletion in 13q as potentially fetal, and invasive testing by amniocentesis was offered as this chromosome aberration can be associated with severe fetal malformations, depending on the exact breakpoints. These uncertainties led to a lot of stress for the parents. With prior knowledge of a maternal CLL, the patient and clinicians could have jointly opted to forgo invasive diagnostic testing as the detection of an aberration would likely have reflected the maternal hematological condition rather than a fetal chromosome aberration. As tumor cfDNA can mask fetal cfDNA, there is a considerable risk that NIPT will not provide an accurate assessment of the fetus. Therefore, in all cases of maternal malignancy where cytogenetic evaluation of the fetus is desired, amniocentesis should be recommended.

Our findings underline that NIPT is not advisable for pregnant women with confirmed malignancy [10]. In these cases, it can be difficult to accurately interpret the fetal genetic constitution.

Instead of NIPT, a detailed structural anomaly screening by ultrasound and an amniocentesis for karyotyping, if certainty on chromosomal abnormalities is desired, are the most appropriate options in these situations. If parents choose to forgo this invasive testing, they may still consider NIPT, but only after thorough genetic counseling by a

clinical geneticist to ensure that they are aware of the risks associated with abnormal results.

With the advent of novel algorithms that account for the origin of circulating cfDNA, advancements in reliably measuring fetal fraction, and improved methodologies for detecting aneuploidies, future approaches may allow for the identification and exclusion of tumor-derived cfDNA from the NIPT analysis. Thereby reducing the risk of misdiagnoses [9]. Until then, NIPT testing in patients with malignancies should be avoided.

AUTHOR CONTRIBUTIONS

Jorn Assmann: writing—original draft preparation. **Diane van Opstal**: writing; visualization. **Karin Diderich**: resources; visualization. **Nicole Larmonie**: writing; visualization. **Yorick Sandberg**: resources; supervision; writing—review and editing. **Yorick Sandberg**: had full access to all the data in the study and takes responsibility for the integrity of the data.

CONFLICT OF INTEREST STATEMENT

The authors do not report any potential conflicts of interest, including relevant financial interests, activities, relationships, and affiliations (e.g., employment, affiliation, grants or funding, consultancies, honoraria or payment, speakers' bureaus, stock ownership or options, expert testimony, royalties, donation of medical equipment, or patents planned, pending, or issued) with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are not publicly available due to privacy. However, they can be made available upon reasonable request from the corresponding author. Requests will be evaluated in complience with applicable data sharing policies and regulations.

ETHICS STATEMENT

This study was conducted in accordance with the ethical principles and guidelines established by the Declaration of Helsinki.

FUNDING INFORMATION

The authors received no specific funding for this work.

PATIENT CONSENT STATEMENT

Informed consent was obtained from the patient prior to their inclusion in this study. The patient was provided with detailed information about the purpose, procedures, risks, and potential benefits of the research. The patient was given the opportunity to ask questions and was assured that participation was voluntary and that the patient could withdraw at any time without penalty. The patient was informed that data would be anonymized and kept confidential, with personal identifiers removed prior to analysis and publication. The study procedures and use of personal data were in compliance with the relevant data protection laws and institutional guidelines. By signing the informed consent form, the patient acknowledged understanding of the study's aims and willingness to take part in the research. A copy of the consent form was provided to the patient for her records.

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