NIPT Incidental Results: Suggestive of Malignancy

Recommendations of Practice

Background

Non-invasive prenatal tests (NIPT) uses placental cell free DNA (cfDNA) to screen for fetal aneuploidy and genetic differences. However, there are several biological confounders which could result in a discordant result. These confounders include placental mosaicism, maternal aneuploidy or mosaicism, organ transplantation and maternal malignancy[1].

The purpose of this document is to describe an investigative approach when a NIPT result comes back suggestive of maternal malignancy.

Circulating tumour DNA (ctDNA) is a subset of cfDNA. It is derived from apoptotic or necrotic tumour cells shed into the maternal circulation. This can result in a reading of multiple chromosomal aberrations (gains and losses) which can be indicative of maternal malignancy. These copy-number abnormalities (CNAs) are spread across the genome. Labs who target three chromosomes for aneuploidy screening have limited ability to detect CNAs as they do not analyse segmental change across the genome, however, whole-genome sequencing is more like to detect this variation.

The incidence of multiple CNAs on NIPT at a population level is 0.008-0.003%[1-3].

Maternal malignancy in pregnancy is rare with an incidence of 1 in 1000-2000 pregnancies[4]. The incidental detection of cancer by the way of NIPT has the potential to improve outcome and institute earlier management with respect to an earlier cancer diagnosis.

The sensitivity and specificity of NIPT in the detection of malignancy in a general population is currently unknown[5]. However, the positive PPV for malignancy when a NIPT reports “significant CNAs” is 30-90%[1,5-7].

It is important to recognise that a low-risk screen result should not be interpreted as a negative screen for malignancy as 85-90% of maternal cancers are unable to be detected on NIPT[7].

Recommended management model

- Ensure before any investigation that a second NIPT test is taken to confirm the presence of CNAs.
- The majority of cancer detected via NIPT have been metastatic and been detected in advanced cancer stages. Patients may be presymptomatic or have clear symptomatology both of which can overlap with pregnancy symptoms. A careful step-wise investigative approach is required. Thorough history and examination is advised including: breast, skin, lymph node, cardiorespiratory, abdominal, vaginal and rectal examination[1].
- Tumour size, type and proliferation status might determine the degree of cfDNA shedding into the maternal circulation5. The types of cancers subsequently detected after a NIPT has shown multiple CNAs include1-3,6,8,9:
- Solid organ:
    - Cervical cancer
    - Breast Cancer
    - Cancers with metastases
        - Colon cancer with liver mets
        - Colon cancer with vertebral mets
        - Sigmoid cancer with vertebral mets
        - Rectal cancer with liver mets
        - Melanoma with liver mets
        - Lung cancer with brain mets
        - Breast cancer with mediastinal mets
        - Breast cancer with positive lymph nodes
        - High-grade neuroendocrine small-cell carcinoma
        - Leiomyosarcoma
        - Carcinoma with unknown primary
- Haematological
    - Classical Hodgkin lymphoma
    - Hodgkin lymphoma with widespread metastatic disease
    - Nodular sclerosis Hodgkin lymphoma
    - Mediastinal large B-cell lymphoma
    - Activated B-cell type diffuse large B-cell lymphoma with bone mets
    - Lymphoma
    - Acute Myeloid leukaemia
- False positive1,3,5,10,11
    - Degenerative uterine leiomyoma
    - Cell lysis
        - Congenital haemolyisis, familial Mediterranean fever
    - Use of heparin in pregnancy
    - Autoimmune disease (eg SLE)
    - Vanishing twin
    - Vitamin B12 deficiency

Genetic Lab advice

- The genetics lab will be able to provide guidance as to whether the cfDNA is more in keeping with a solid (eg colorectal, melanoma) or haematopoietic (eg lymphoma, leukaemia) malignancy.

Staged Investigation

First Line

- CXR with abdominal shielding
- USS: breast/liver
- Bloods
  - FBC, U+E, LFT, LDH, AFP, CEA, Ca125, CA 15-3, CA 19-9
- Cervical smear+/-colposcopy

Consider maternal microarray on DNA extracted from maternal lymphocytes.
Additional targeted investigations as determined by history and examination.

Second Line

- Referral to Oncology disciplines
- MDT approach including:
  - Clinical Geneticists, Medical Oncology disciplines, MFM specialists, Neonatologists, Pathologists and Radiologists

- WB-MRI if first line imaging negative.

- Consider following if WB-MRI negative[1]:
  - Low dose ^{18}FDG PET-CT **
    - Useful in confirming or excluding malignancy
    - Radiation dose, 1.1-2.43 milliGray, is lower than diagnostic C (7-10 milliGray)
    - Reduced further by adequate hydration and frequent voiding

  - Digital PET-CT or non-contrast ^{18}FDG PET-MRI maybe an alternative where available.

Cancer diagnosis

Management and treatment will be guided by malignancy location and staging as well as pregnancy gestation. This may include the difficult discussion about pregnancy termination or a planned premature delivery in order to facilitate aggressive cancer treatment. A MDT approach involving Maternal Fetal Medicine and Oncology is recommended in all cases.

Consideration should be given to the patient's future fertility as some treatments will have a detrimental effect on fertility. This may require an urgent consultation with a Reproductive Endocrinologist with a specialty interest in this area.

Negative investigation

This maybe be a false negative case. Consideration could be given to a benign or transitory diagnosis such as a degenerating uterine leiomyoma or vanishing twin (see false positive list above). Ongoing management should be guided by an MDT approach with close clinical monitoring.

Consideration should be given to:

- Repeating the NIPT in 10-12 weeks post the initial result to see if there are any CNA changes or resolution.
- The NIPT should be repeated postnatally to ensure either resolution of findings or persistence of abnormal CNAs.
- If CNAs are persistent postnatally, consideration should be given to further investigations under guidance from Oncology.

Completing the aneuploidy screen

The NIPT cannot give a determination of risk of chromosomal difference. The completion of this screening test should be offered. A morphological assessment of the fetus should be undertaken with an offer of a CVS or amniocentesis with testing for chromosomal microarray.

Support for patient and their whānau

It can be distressing for someone to hear they may have a possibility of cancer, especially when the test ordered was not for that purpose. It is essential to offer holistic and wrap around care for the patient and whānau. This may include counselling and early referral to cancer nurse co-ordinators or CNS Maori if relevant.

This Recommendation of Practice was updated in December 2023 by Dr Jaynaya Marlow with input from members of Wāhi Rua NZMFM Network.

The most up to date version of this Recommendation of Practice can be found on Healthpoint Wāhi Rua: New Zealand Maternal Fetal Medicine Network (NZMFM) webpages: https://www.healthpoint.co.nz/public/wahi-rua-new-zealand-maternal-fetal-medicine/

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