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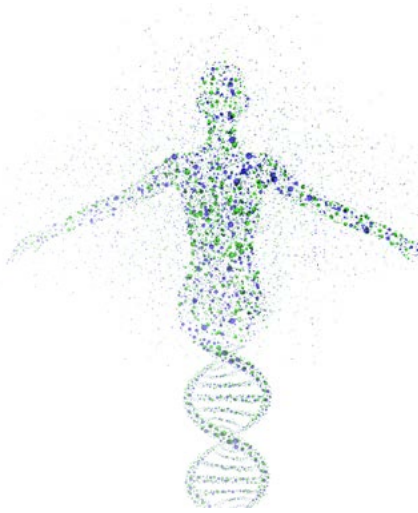
PERSONALISED MOLECULAR DIAGNOSTICS > FOR SOMATIC DISEASE > FOR YOU

Cell-Free Tumour DNA Testing in Cancer



A biomarker is a chemical compound that can be used to monitor disease. For cancer, the aims of a sensitive biomarker are to enable early detection of cancer, monitoring of disease progression and response to treatment.

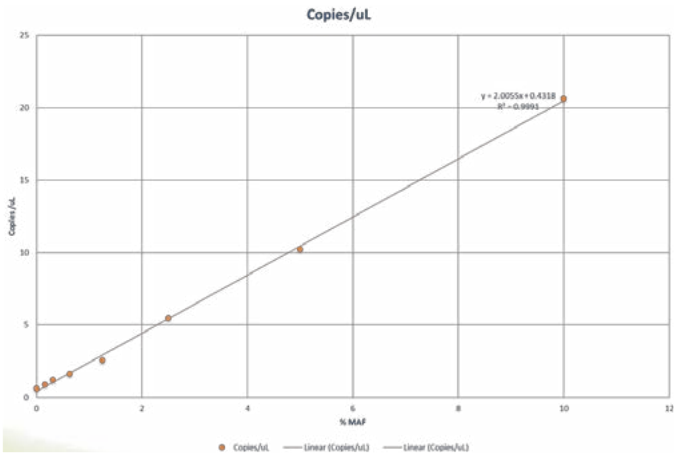
During the 1900s a number of chemicals (proteins, enzymes and hormones) were identified in biological fluids from cancer patients, however monitoring of malignant diseases essentially started with the identification of two biomarkers (alpha-fetoprotein and carcinoembryonic antigen) in the 1960s.

Biomarker discovery in cancer has rapidly proliferated and thousands of biomarkers have been described, but relatively few are in clinical use. In some cases this may relate to technical challenges in the testing itself, but is usually due to overlap of ranges between normal and cancer patients so that normal and cancer patients cannot be clearly separated from each other.

A solution to these problems has now been found with the development of new technologies and techniques including sequencing technologies, massive parallel sequencing and highly sensitive quantitative polymerase chain reaction (PCR) testing.

International collaborative projects including the International Cancer Genome Consortium and the Catalogue of Somatic Mutations in Cancer (COSMIC) have identified driver mutations (errors in DNA in tumours) in multiple cancer types that cause the tumour to develop and grow. These mutations are only present in tumour cell DNA (somatic mutations) and are not present in normal cells. This provides an extremely specific biomarker for cancer that can be detected and tracked over time.

Currently the standard approach for cancer diagnosis is the examination of tumour tissue through either removing cells through a small needle (fine needle aspiration cytology), or histological examination of a biopsy or surgical excision specimen. These procedures are invasive and involve some risk to the patient. In some cases, biopsy is also not possible due to the location of the tumour.



RIGHT: Limit of detection curve showing copies of ctDNA in a background of normal DNA.

Genetic Testing

Genetic testing is available for ctDNA in blood. DNA is extracted from plasma and highly sensitive testing is then used to detect specific DNA mutations in the circulating cell-free tumour DNA.

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Cell-Free Tumour DNA in Cancer

Cell-free DNA (cfDNA) is released from normal cells and tumours by programmed cell death (apoptosis)

- cfDNA comprises small fragments of nucleic acid that are not associated with cells or cell fragments.
- cfDNA is present in the plasma of blood in all people.
- Tumours containing ~ 50 million malignant cells release sufficient DNA for the detection of circulating cell-free tumour DNA (ctDNA) in blood. [1]
- In comparison, the limit of resolution for radiology studies is a tumour size of approximately 7 – 10 mm in size and containing ~1 billion cells.
- As the volume of the tumour increases, the number of apoptotic and dead cells increases due to increased cellular turnover.

Applications of cfDNA Testing

Circulating tumour DNA fragments (ctDNA) contain identical genetic defects to those seen in the primary tumour itself. [2]

Because ctDNA fragments are released from all parts of the tumour the ctDNA is in fact a liquid biopsy. [2]

Monitoring of tumour burden. [3–9]

Monitoring of minimal residual disease

- ctDNA is a potential marker of residual disease after surgery and should be measured after the surgery but before the commencement of adjuvant therapy (generally 6-8 weeks after surgery). [2]

Monitoring of molecular resistance

- Liquid biopsies can be used to monitor the development of resistance to therapy during treatment [2].
- This understanding of the mechanisms of resistance can be used to plan combination treatment and institute alternate therapies.

Monitoring of tumour heterogeneity

- ctDNA analysis can provide an overview of all the cells in a patient's tumour simultaneously and this takes into account variations in different cells in the tumour and may provide an early indication if cells are becoming resistant to therapy.
- In addition, mutations in different pathways in the tumour cells can be used to plan combination treatment and this approach can prevent resistance developing in the tumour cells and improve response [10].

Early diagnosis of tumours

- The new tests open up the possibility of using ctDNA for screening in the future.

Genetic Testing

- The development of sensitive and specific tests for the detection of circulating cell-free DNA on blood samples means that patients with tumours can now be monitored over time to assist in the assessment of response to treatment.
- The testing is specific to each individual's tumour and forms part of personalised medicine.

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