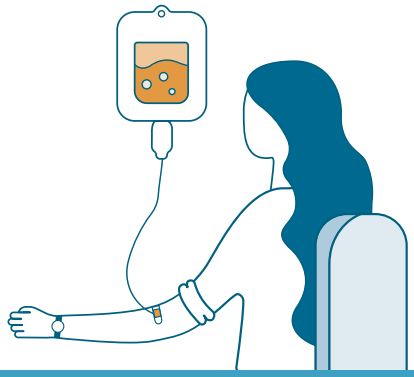
Research Findings Brief

HEALTHIER LIVES | He Oranga Hauora | National Science Challenges



CtDNA for better cancer management: applying precision oncology to the New Zealand healthcare system

Key points

- Undergoing cancer treatment can be traumatic, difficult and time-consuming for patients, and there are inequities in cancer treatment in the current healthcare system.
- CtDNA technology is a ground-breaking method of testing and monitoring cancer treatment progress that uses simple blood tests to identify and measure cancer markers in the bloodstream, and has the potential to change how cancer is managed.
- The Healthier Lives ctDNA project has established that the use of ctDNA technology in the New Zealand healthcare system will enable timelier and less invasive testing and monitoring of cancer treatment, and could contribute to better outcomes and improved equity.
- CtDNA technology has important implications for the health system in the form of reducing inequities, improving access and reducing costs.

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PROJECT TIMELINE

November 2015 – June 2019

We tested ctDNA technology as a tool for detecting two of NZ's most prevalent cancers (colorectal cancer, melanoma).

We found that ctDNA technology is more sensitive and responsive than other detection tools currently in use.

Developing ctDNA technology for cancer detection matters because patients will receive better treatment for their individual circumstances.

Why is this issue important?

> “CtDNA is not simply a diagnostic test, but a disruptive technology at the vanguard of precision medicine. It brings with it the potential for broad changes in how cancer is treated day to day, and has numerous potential applications in the care of individual patients.”

Better treatment

Integrating routine ctDNA measurements into treatment plans will mean better treatment for individual patients through:

- identifying changes in tumour mutations over time, indicating the most effective treatment combination for each patient at each stage of their disease – a new level of personalised medicine
- earlier termination of futile treatment, leading to less toxicity and more rapid responsiveness to the emergence of drug resistance
- earlier detection of relapse.

More nimble treatment

CtDNA has potential to lead to more responsive treatment trials. Because ctDNA can rapidly determine whether a treatment is effective (in around 2 weeks rather than the traditional 6-12 weeks required when CT scans are used), it may provide the opportunity to trial new drug regimens and rapidly swap them out if they are ineffective.

This will lead to a rapidly learning system, rather than having to rely on the slow-moving results from large population-based clinical trials, as often happens now.

Better cancer care systems

The use of ctDNA as a diagnostic and surveillance tool will lead to increased community-based cancer management, reducing pressure on hospital services (e.g. radiology departments) and improving access to healthcare for rural, Māori and Pasifika populations, since it can be done in remote locations such as marae clinics and remote islands.

If developed in partnership with cancer services, the simplicity and accessibility of blood tests can lead to reduced cost, reduced inequity and more effective patient care.

What did we do?

We conducted two prospective flagship studies using ctDNA:

Colorectal cancer

We assessed the utility of ctDNA as a tool to rapidly identify changes in tumour burden in 60 colorectal cancer patients who were undergoing chemotherapy for metastatic disease or were under surveillance following surgery.

Melanoma

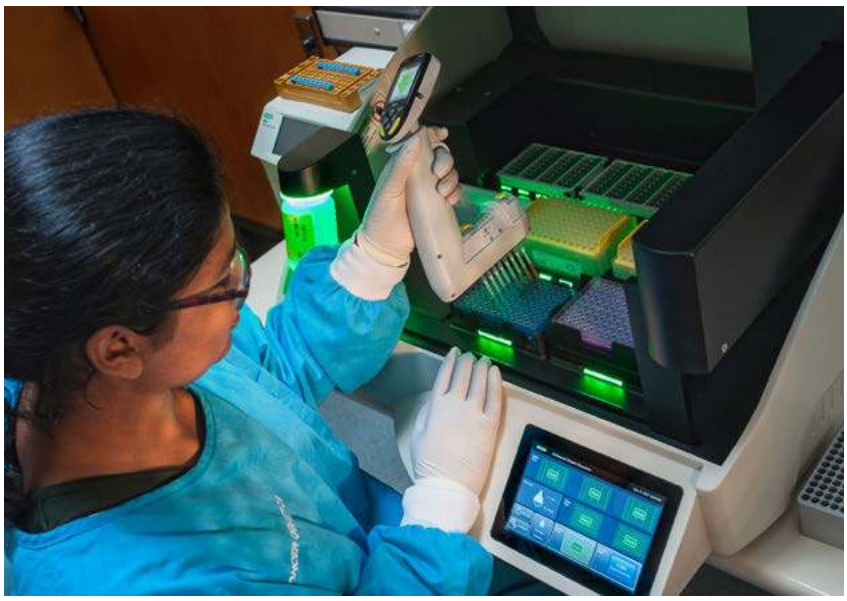
We investigated whether minimally invasive blood sampling followed by plasma DNA analysis can inform treatment for patients with metastatic melanoma.

- The two studies established and compared ctDNA methodology on a range of analytical platforms (droplet digital PCR, mass spectroscopy and next generation sequencing) and demonstrated its utility for the management of advanced colorectal cancer and melanoma.
- We demonstrated the feasibility of collecting samples from remote locations by showing that blood samples collected into special tubes are stable for at least one week.
- We established a collaboration with Canterbury Health Laboratories and Grafton Clinical Genomics to accelerate implementation of ctDNA technology.
- In partnership with Genomics Aotearoa, we built a prototype of the bioinformatics pipeline which is needed to ensure consistent laboratory testing procedures.

What did we find?

The two studies showed that:

- the minimal gene sequencing panel for colorectal cancer ctDNA is KRAS, TP53, BRAF and APC, and for melanoma it is TERT, NRAS, BRAF;
- 97% of colorectal cancer patients and around 80% of melanoma patients with metastatic disease had detectable ctDNA using the studies' methodologies (while only 77% of colorectal cancer tumours in the study could be tracked with CEA);
- ddPCR ctDNA measurements are stable and rapidly responsive to treatment change – the effect of changes in drug type, dose or timing on tumour burden were frequently detected after only two weeks;
- ctDNA measurements using ddPCR (and, in some cases, sequencing) could be turned around in 3 days, which is rapid enough for routine clinical use;



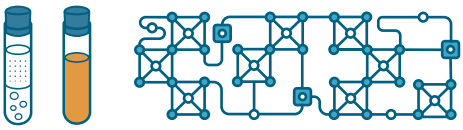
- blood samples collected in either Roche or Streck ctDNA tubes are of sufficient quality for later ctDNA analysis using both ddPCR and sequencing, providing a sufficient time window for remote collection;
- a melanoma-specific Ampliseq HD sequencing panel covering the 35 genes frequently mutated in melanoma has comparable sensitivity to ddPCR;
- ctDNA can be used for:
  - + identification of patients who may benefit from targeted therapies
  - + surveillance of patients for relapse after surgery, and
  - + probably also for early confirmation that melanoma immunotherapy is effective, as well as early identification of disease progression.

What is ctDNA?

Circulating tumour DNA (ctDNA), sometimes termed 'liquid biopsy', is an emerging technology which is transforming the field of cancer personalised medicine.

Every tissue in the body – including cancers – have cells which die every few days. When those cells die, their DNA gets spilled into the bloodstream. The DNA from tumours can be recognised through the presence of mutations in the DNA sequence. CtDNA uses simple blood tests to detect this tumour DNA.

CtDNA means scientists can identify genes involved in cancer behaviour, and the mutations in those genes. By quantifying the number of mutated DNA molecules in the blood stream they effectively have a measure – or a marker – of the size of a cancer. Changes in the levels of these markers can indicate the growth or shrinkage of tumours.



What did we produce?

- Colorectal cancer surveillance assay
- Melanoma surveillance assay
- Bioinformatics pipeline

Publications

Circulating tumor DNA is a sensitive marker for routine monitoring of treatment response in advanced colorectal cancer *Carcinogenesis* 2020; 41(11), 1507–1517. doi: 10.1093/carcin/bgaa102

Comparison of Roche Cell-Free DNA collection Tubes® to Streck Cell-Free DNA BCT®s for sample stability using healthy volunteers *Practical Laboratory Medicine* 2019; 16:e00125. doi:10.1016/j.plabm.2019.e00125

Why does it matter?

Here's what integrating ctDNA technology into New Zealand's health care system could mean for a cancer patient

More targeted treatment

Patients' treatment plans can be personalised depending on their response to treatment.

Testing closer to home

The blood test can be done in a local clinic, including marae clinics, without the need to travel to a hospital.

More timely testing

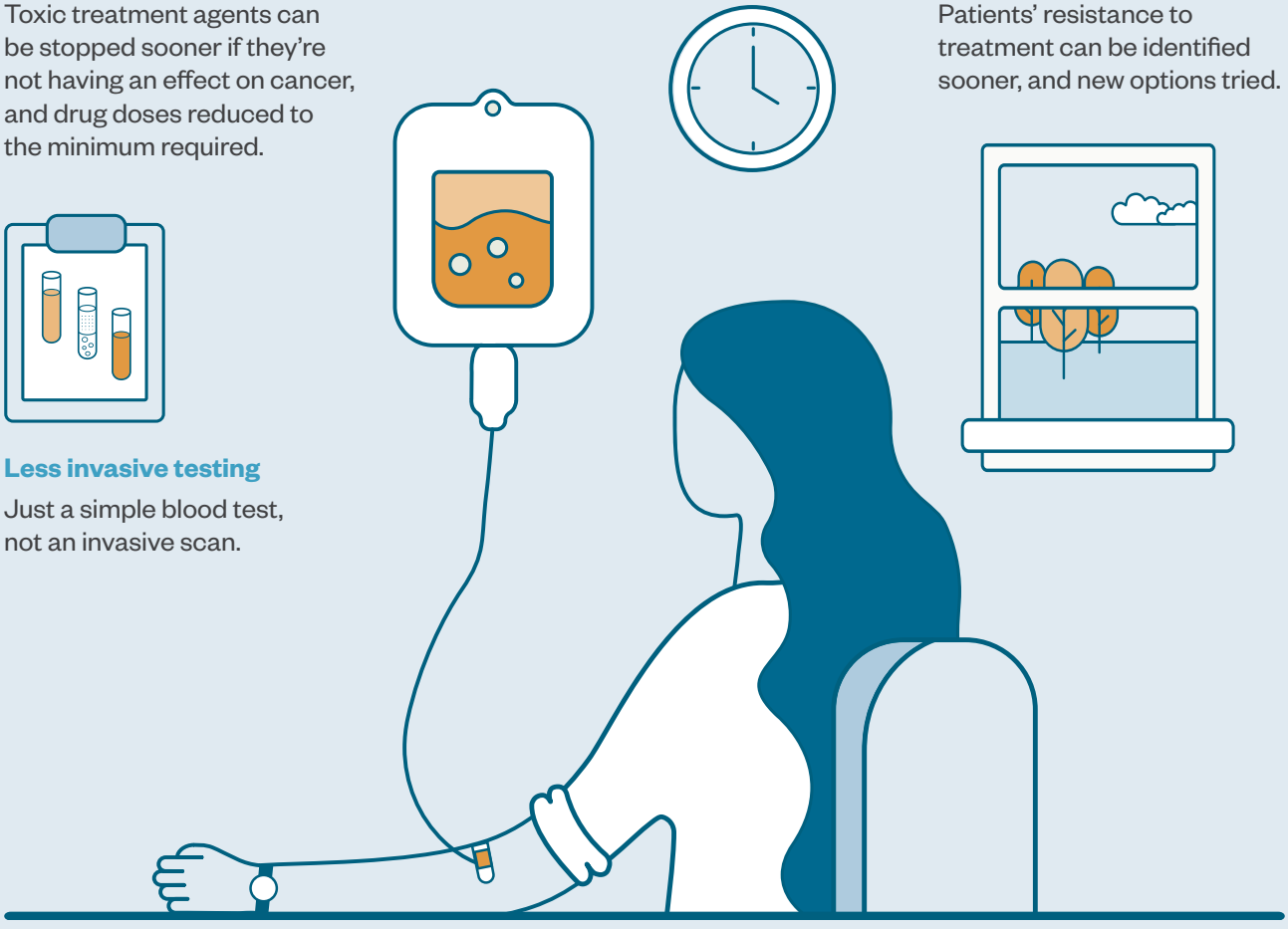
Patients can be tested after 2 weeks of treatment, rather than 6-8 weeks.

Fewer treatment side effects

Toxic treatment agents can be stopped sooner if they're not having an effect on cancer, and drug doses reduced to the minimum required.

Better long-term treatment

Patients' resistance to treatment can be identified sooner, and new options tried.



Less invasive testing

Just a simple blood test, not an invasive scan.

Next steps

We will broaden the technology to other cancer types, including breast, lung, stomach and paediatric cancers.

We will engage with a wider range of stakeholders, including Māori primary healthcare providers, with the goal of demonstrating the utility of ctDNA technology in different New Zealand clinical settings.

In parallel, we will collaborate with accredited diagnostic laboratories (Canterbury Health Laboratories and Grafton Clinical Genomics) to establish the technology as a routine, validated clinical service.

Finally, we will establish a New Zealand ctDNA Collaboration Network to lead the coordinated implementation of ctDNA technology into the New Zealand healthcare system and facilitate the entry of new research groups into the field.

Acknowledgements

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Research team

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About Healthier Lives

National SCIENCE Challenges

HEALTHIER LIVES

He Oranga Hauora

Our vision is of Aotearoa New Zealand with equitable health outcomes and a substantially reduced burden of non-communicable diseases.

Tō mātou kitenga kia noho a Aotearoa New Zealand hei whenua he ōrite ngā putanga hua hauora mō te tangata, kia iti iho hoki ngā pīkauranga o ngā māuiui kāore e taea te tuku ki te tangata kē.

The **Healthier Lives – He Oranga Hauora National Science Challenge** is a national collaborative research programme, investigating innovative approaches to the prevention and treatment of four major non-communicable diseases (NCDs) – cancer, cardiovascular disease, diabetes and obesity.

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University of Otago, Massey University, University of Canterbury, ESR, University of Waikato, AUT, Malaghan Institute, AgResearch, Victoria University of Wellington, University of Auckland

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