

# Circulating tumour DNA technology: the future of cancer management?

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Cancer incidence is increasing worldwide and in the UK it is estimated that 1 in 2 people born after 1960 will be diagnosed with some form of cancer in their lifetime. Could circulating tumour (ct) DNA technology help the health system meet the challenge of this cancer burden, and what needs to be done to maximise its utility?

## Key facts

-  As tumour cells die they release fragments of DNA into the patient's bloodstream - this is known as circulating tumour (ct) DNA
-  Clinicians can use ctDNA to learn about the genetics of a patient's tumour; this information can aid cancer management
-  ctDNA is extracted from a blood sample and analysed using genomic technologies including PCR, exome sequencing and whole genome sequencing
-  Taking a blood sample - a 'liquid biopsy' - is less invasive than a solid tumour biopsy, and so can be used throughout treatment, as well as for patients in whom a tissue biopsy is difficult or impossible
-  Liquid biopsies have several other advantages over traditional biopsies, such as capturing tumour diversity. But they also have disadvantages, one being that they cannot be used for diagnosis since the tumour tissue of origin cannot be determined
-  ctDNA liquid biopsies can be used to make treatment decisions, such as whether patients are eligible for certain therapies, based on the genetic profile of their tumour

## What is ctDNA and how is it measured?

As cells within the body die and are broken down, fragments of DNA are released into the bloodstream. If a patient has cancer, their bloodstream can contain both DNA from their normal cells and DNA from the cells in their tumour - circulating tumour DNA.

Analysis of ctDNA requires sensitive scientific techniques that are able to detect very small amounts of ctDNA among the non-cancerous DNA in a blood sample. These include next generation sequencing technologies such as exome sequencing and whole genome sequencing, and other methods such as PCR.

## What can ctDNA liquid biopsies be used for?

### Making treatment decisions

New classes of cancer drugs - biological therapies - have been developed that target tumours with particular genetic mutations. A liquid biopsy can help determine whether patients are eligible for these therapies.

#### Case study

Tyrosine kinase inhibitor drugs can be used on patients with non-small cell lung cancers with mutations in a gene called *EGFR*. A liquid biopsy can determine whether a patient carries mutations in the *EGFR* gene, and if they can be treated with these drugs.

### Monitoring emergence of resistance mutations

Should a patient stop responding to a therapy, a liquid biopsy can be used to determine if the tumour has developed mutations that confer resistance to that therapy.

### Monitoring treatment response and relapse

Liquid biopsies can also help to monitor treatment effectiveness, since if a treatment is successful ctDNA levels ultimately fall to undetectable levels.

#### Case study

Regular monitoring of ctDNA in the blood in a group of breast cancer patients showed that the emergence of mutations in ctDNA predicted relapse months before other clinical evidence of relapse.

### Cancer screening

Liquid biopsies could potentially be used for screening purposes, particularly in high risk groups. However, this is a long way from implementation due to challenges including the risk of overdiagnosis and lack of evidence to show that early detection of cancer in this way results in better outcomes for patients.

## Benefits of ctDNA liquid biopsies

### Increase accessibility of testing

All of the tests outlined in the previous section can also be carried out on solid tumour samples but solid tumour biopsies can be difficult or impossible to carry out, sometimes causing harmful side-effects. Liquid biopsies are less invasive and easier to carry out, meaning that more measurements can be made without placing too much of a burden on patients. This makes cancer genetic testing accessible to more patients and also enables clinicians to build up a more accurate picture of how tumour genetics change over time.

### Capture tumour diversity

Cancer is a genetically diverse (heterogenous) disease, and capturing this diversity can be challenging, particularly if tumours have spread. Liquid biopsies can potentially capture tumour heterogeneity more accurately than isolated solid biopsies, as they measure ctDNA from multiple sites in the body.

## Disadvantages of ctDNA liquid biopsies

### Biological factors

Some cancers release more ctDNA than others and so are more amenable to the use of ctDNA technology, for reasons that are not yet fully understood.

### Clinical utility

It is not yet clear whether using ctDNA testing improves patient care and outcomes. Work is being carried out to collect this information. Currently ctDNA testing is only used when the result can be used in clinical decision making.

### Cost implications

While ctDNA testing can be used to offer more personalised treatment, it is not clear if a more personalised approach saves the health service money.

### Diagnostic limitations

Solid tumour biopsies remain the gold standard for diagnosis; liquid biopsies are unsuitable since the tumour's tissue of origin cannot be determined. Currently, ctDNA testing complements conventional methods.

## Current use of ctDNA liquid biopsies

While research and early-phase clinical trials have demonstrated that ctDNA testing can be used to monitor tumours and make treatment decisions in a range of cancers, clinical application is currently limited. Liquid biopsy is currently being offered or is being developed in a small number of UK laboratories to determine *EGFR* status in non-small cell lung cancer, in order to make treatment decisions in some patients.

## What is needed to maximise the utility of ctDNA liquid biopsies?

-  Incorporation into current clinical pathways  
Can ctDNA testing fit into current testing pathways? What additional changes need to be made to ensure that samples are collected correctly and delivered to the lab in a timely manner? Can ctDNA testing be delivered at a cost and within a timeframe comparable to solid tumour testing?
-  Critical evaluation of patient impact  
If ctDNA testing is used to inform drug selection, will this result in improved patient outcomes in terms of progression-free survival?
-  Standardisation of techniques and sharing of best practice  
What technique(s) and equipment work most reliably in a clinical setting? Are data analysis techniques consistent and reliable?
-  Support genetics service providers to develop testing  
What are the infrastructure requirements in terms of laboratory space, equipment and expertise?
-  Engagement of stakeholders  
Engage service providers, oncologists and other health system staff about ctDNA testing and its advantages and limitations.
-  Research and evidence collection  
To determine the greatest areas of clinical unmet need that ctDNA testing can address.

To find out more, visit:  
[www.phgfoundation.org/project/ctDNA](http://www.phgfoundation.org/project/ctDNA)

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