NICE advice

Signatera for detecting molecular residual disease from solid tumour cancers

Medtech innovation briefing
Published: 4 October 2022

www.nice.org.uk/guidance/mib307

Summary

- The **technology** described in this briefing is Signatera. It is used for measuring circulating tumour DNA (ctDNA) in the body to detect the presence of molecular residual disease (MRD) from solid tumours.
- The **innovative aspects** are that Signatera is designed to detect and track tumour-specific clonal mutations with a low limit of detection. This may optimise sensitivity for more accurate MRD assessment.
- The intended **place in therapy** would be in addition to standard care in people with solid tumour cancers. It can be used in the adjuvant setting to inform the need for additional treatment after surgery, and the surveillance setting to monitor for recurrence or assess therapy response.

- The **main points from the evidence** summarised in this briefing are from 6 studies (4 prospective cohort studies, 1 phase 2 trial, and 1 secondary analysis from a randomised phase 3 trial) including 1,102 people with solid tumours. They show that Signatera improves prognostic assessment and may detect recurrence earlier than standard care alone. ctDNA testing with Signatera may also predict response to adjuvant treatment.
- **Key uncertainties** around the evidence or technology are that there is no prospective evidence on using Signatera in clinical practice or its effect on treatment decisions or clinical outcomes.
- **Experts advised** that there is not enough evidence to support routine use of the technology in the NHS. This is in line with recommendations from the European Society for Medical Oncology on the use of ctDNA. But there are several ongoing trials that may address gaps in the evidence.
- The **cost** of Signatera is between £2,900 and £3,500 per test (excluding VAT). Costs may be offset if it reduces the use of adjuvant therapy or imaging. But some experts cautioned that they would not offer treatment without radiographic results, which could lead to increased imaging.

The technology

Signatera (Natera) is a personalised molecular residual disease (MRD) assay that measures circulating tumour DNA (ctDNA) in the body. It is intended to help identify ctDNA in people with solid tumours, including colorectal, breast, bladder, renal and lung cancer. ctDNA is a type of cell-free DNA (cfDNA) that can suggest the presence of cancer cells.

Initial testing requires samples of a person's blood and solid tumour tissue from surgical resection. Signatera sequences the tumour tissue to identify the person's unique signature of tumour mutations. This is used to design a multiplex polymerase chain reaction (PCR) assay targeting 16 patient-specific clonal tumour mutations. Once a personalised assay is designed, subsequent blood samples can be used to monitor the presence or absence of MRD over time and assess disease burden in response to treatment. In NHS settings, patient samples would be collected and shipped to Natera laboratories in the US for Signatera testing. Initial testing takes 2 to 3 weeks, while subsequent tests take around 5 to 7 days from receipt of blood sample to return of results.

Innovations

Experts advised that several ctDNA technologies are being tested across a range of tumour types. Signatera is designed to detect and track tumour-specific clonal mutations with a low limit of detection below 0.01% variant allele frequency. The company said that other ctDNA tests tend to report average variant allele frequency which can be affected by increases in cfDNA unrelated to disease burden. Signatera calculates mean tumour molecules per millilitre, which the company said is more accurate for tracking cfDNA over time. Signatera also filters out clonal haematopoiesis of indeterminate potential and germline mutations to reduce false-positive results.

Current care pathway

Treatment for solid tumour cancers varies depending on the type and stage of cancer. Surgery is often the first treatment because solid tumours can usually be removed. People may also be offered systemic anti-cancer therapy or radiotherapy. Molecular biomarkers may be used to guide treatment decisions. Some people will have residual disease that may cause recurrence of cancer. Adjuvant therapies such as chemotherapy or biological therapy may be offered depending on the cancer stage and grade, and a person's general health. Prognosis and risk classification may be assessed by:

- cancer staging systems such as the TNM staging system
- risk prediction tools such as the PREDICT tool for breast cancer
- tumour profiling tests
- discussing risk and disease progression at multidisciplinary team meetings.

Follow up after treatment is offered to monitor treatment response and to detect recurrence. It may include health checks and clinical assessment, imaging such as CT scans and carcinoembryonic antigen (CEA) tests. Surveillance varies depending on cancer type and risk classification.

The European Society for Medical Oncology (ESMO 2020) guideline for localised colon cancer states that postoperative ctDNA shows some benefit in determining risk of recurrence. ctDNA could be considered in addition to standard care to help make decisions about adjuvant care in difficult cases. ESMO does not recommend the routine use of ctDNA to detect MRD because more evidence is needed on its clinical utility

(Pascual et al. 2022).

The following publications have been identified as relevant to this care pathway:

- NICE guideline on bladder cancer: diagnosis and management
- NICE guideline on early and locally advanced breast cancer: diagnosis and management
- NICE guideline on cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over
- NICE guideline on colorectal cancer
- NICE cancer service guideline on improving outcomes in head and neck cancers
- NICE guideline on lung cancer: diagnosis and management
- NICE guideline on oesophago-gastric cancer: assessment and management in adults
- NICE guideline on ovarian cancer: recognition and initial management
- NICE guideline on pancreatic cancer in adults: diagnosis and management
- NICE guideline on prostate cancer: diagnosis and management
- NICE diagnostics guidance on tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer.

Population, setting and intended user

Signatera is indicated for use in people with solid tumour cancers. There are about 375,000 new cases of cancer each year in the UK. Breast, prostate, lung and bowel cancer make up more than half of new cases.

Signatera would be used in addition to standard care. There are 2 Signatera testing settings depending on which treatment the person has had:

- Adjuvant setting: Signatera can be used in secondary care within 6 months after surgery to evaluate the need for adjuvant therapy. The company proposes that Signatera would be used 2 to 8 weeks after surgery to determine MRD status and to inform if adjuvant treatment is needed. Follow-up testing may be done to increase sensitivity of detecting MRD. People who test MRD-positive and have adjuvant therapy may continue to have follow-up tests every 4 to 8 weeks to monitor treatment response.
- Surveillance setting: Signatera can also be used after the initial 6-month postoperative period to detect recurrence and to monitor treatment response. It would be used alongside follow-up visits and tests for up to 5 years in line with monitoring guidelines.

Costs

Technology costs

Signatera costs between £2,900 and £3,500 per test (excluding VAT). Costs include exome sequencing and design of patient-specific primers. There will be some cost to NHS laboratories to collect and prepare samples for testing.

Costs of standard care

Signatera is an addition to standard care. ctDNA assays such as Signatera are not currently part of standard care for solid tumour cancers in the NHS. Costs of standard care will vary depending on type and stage of cancer.

Resource consequences

Signatera is not routinely used in the NHS. It is an external test and is unlikely to need changes in facilities. Signatera may help identify people whose cancer is at risk of recurrence and for whom adjuvant therapy or escalation of treatment is suitable. This may reduce the use of adjuvant therapy in people whose cancer is lower risk. Signatera may also detect recurrence earlier and while the tumour is potentially resectable and may reduce false-positive results from less sensitive markers. It may therefore increase efficiency by offering the right treatment to people when needed. There is evidence from an Australian payer perspective that ctDNA-informed adjuvant chemotherapy may be cost effective compared with standard care (To et al. 2021). There is no evidence on the

resource consequences of using Signatera in the NHS.

Regulatory information

Signatera is a CE-marked class IVD General in vitro diagnostic medical device under the EU In Vitro Diagnostic Medical Devices Directive (IVDD).

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

No equality issues were identified related to the use of Signatera. Cancer is considered a disability under the Equality Act 2010. Incidence rates in the UK for all cancers combined are highest in people aged 85 to 89 with more than a third of diagnoses each year being in people aged 75 and older. Age and disability are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Six studies are summarised in this briefing including a total of 1,102 people with solid tumour cancers. These included 4 prospective cohort studies, 1 phase 2 trial, and 1 secondary analysis of data from a randomised phase 3 trial. The clinical evidence and its strengths and limitations are summarised in the overall assessment of the evidence.

There are several full-text publications on Signatera which have not been detailed in this briefing for reasons of brevity:

- Retrospective studies in breast (Magbanua et al. 2020), colorectal (Fakih et al. 2022, Loupakis et al. 2021), lung (Abbosh et al. 2017) and gastrointestinal cancers (Zhang et al. 2021), and oesophageal adenocarcinoma (Ococks et al. 2021).
- Case reports in colon (Weinberg et al. 2021) and colorectal cancers (Schneider et al. 2021) and a case series in people with cancer who are pregnant or planning to become pregnant (Cohen et al. 2022).

Overall assessment of the evidence

Signatera has a large evidence base including many full-text papers and abstracts. The studies summarised in this briefing used prospective collection of samples and provided detailed methods and descriptions of findings. All circulating tumour DNA (ctDNA) analysis was retrospective and healthcare professionals and patients were blinded to test results. There is therefore no evidence on using Signatera in clinical decision making or treatment choice.

The evidence suggests that Signatera could improve prognostic assessment and may detect recurrence earlier than standard care alone. ctDNA testing with Signatera may also predict response to adjuvant treatment. The evidence base would benefit from more prospective studies comparing the concurrent use of Signatera with standard care tests and imaging in larger sample sizes. Only 1 study was done entirely in the UK (Coombes et al. 2019) and more evidence is needed on the use of Signatera in the NHS. Future studies should also include randomised trials evaluating the use of Signatera in clinical practice, including its effect on treatment decisions, outcomes and resource use. There are ongoing studies that may address some of these areas.

Henriksen et al. (2021)

Study size, design and location

Prospective cohort study evaluating the clinical utility of ctDNA assessment in 168 people with stage 3 colorectal cancer at 7 centres in Denmark and Spain.

Intervention

Signatera in addition to standard care. Samples for ctDNA analysis were collected at diagnosis, after surgery, during adjuvant therapy and at follow up.

Key outcomes

Recurrence occurred in 25% of people. Before surgery, 139 of 153 samples (91%) were ctDNA-positive. This reduced to 20 of 140 samples (14%) after surgery before adjuvant chemotherapy. The recurrence rate was 80% for people who tested ctDNA-positive and 18% for people who tested negative.

People with recurrence who tested ctDNA-negative had higher cfDNA than people who tested positive. Authors suggested surgical trauma could increase cfDNA release, which could potentially dilute ctDNA levels below the detection level. For this group, samples taken more than 2 months after surgery had lower levels of cfDNA than those taken at 2 weeks, with the ctDNA detection rate increasing from 0% to 80%.

People who tested ctDNA-positive postoperatively had shorter recurrence-free survival than those who tested negative (hazard ratio [HR] 7.0, 95% confidence interval [CI] 3.7 to 13.5; p<0.001). A multivariable cox regression showed ctDNA was the strongest predictor of recurrence-free survival (HR 30.97, 95% CI 10.6 to 90.2; p<0.001). Overall, 93 people had adjuvant therapy, with persistence of ctDNA after adjuvant therapy associated with shorter recurrence free survival (HR 50.8, 95% CI 15.4 to 167; p<0.001). Serial ctDNA analysis every 3 months detected recurrence with a median lead time of 9.8 months compared with standard care CT scans.

Strengths and limitations

Patients and healthcare professionals were blinded to the ctDNA result, so the study does not show how results may have affected treatment decisions on adjuvant chemotherapy.

Powles et al. (2021)

Study size, design and location

Secondary analysis in 581 people who had surgery for muscle-invasive urothelial carcinoma. This study evaluated outcomes from a subgroup of 809 people in a global randomised phase 3 trial comparing adjuvant atezolizumab (n=406) with observation (n=403) for operable urothelial cancer (Bellmunt et al. 2021 [IMvigor010]). This study included centres from the UK.

Intervention

Signatera in addition to standard care in people having adjuvant atezolizumab or observation. Plasma samples were collected after surgery at baseline and 6 weeks after randomisation to treatment.

Key outcomes

At baseline, 214 people (37%) tested ctDNA-positive. People in the observation arm who tested ctDNA-positive (n=98) had significantly higher risk of disease recurrence than those who tested negative (disease-free survival HR 6.3, 95% CI 4.45 to 8.92; p<0.0001).

People who tested ctDNA-positive at baseline who went on to have adjuvant atezolizumab had better overall survival than those having observation (HR 0.59, 95% CI 0.41 to 0.86, median 15.8 months compared with 25.8 months). The benefit from adjuvant atezolizumab was not seen in people who tested ctDNA-negative (HR 1.31, 95% CI 0.77 to 2.23).

Change from ctDNA-positive to negative across the 2 timepoints was reported in 18.2% of people (18 of 99) who had adjuvant atezolizumab compared with 3.8% (3 of 79) in the observation arm. People who were no longer ctDNA-positive after having adjuvant atezolizumab had better disease-free survival (HR 0.26, 95% CI 0.12 to 0.56; p=0.001) than those who still tested positive.

Strengths and limitations

This study had a reasonably large sample size which included 214 people who tested ctDNA-positive. It suggests that ctDNA-positive results may predict benefit from adjuvant atezolizumab. But ctDNA results were not used to guide treatment decisions and therefore did not affect clinical outcomes. Authors reported 2 timepoints which is less than other studies reporting serial ctDNA analysis. The manuscript was written with some co-authors from the company, but the company said the study was done independently.

Bratman et al. (2020)

Study size, design and location

Phase 2 trial in 106 people with solid tumour cancers who had pembrolizumab in Canada. The study included 5 cohorts: squamous cell cancer of head and neck, triple-negative

breast cancer, high-grade serous ovarian cancer, malignant melanoma and mixed solid tumours.

Intervention

Signatera in addition to standard care in people having pembrolizumab. Samples were collected at baseline and before every 3 cycles of treatment.

Key outcomes

Overall, 94 people had enough tumour tissue for ctDNA analysis. Baseline ctDNA was found in 92 samples (98%). People with breast cancer and mixed solid tumours had the highest ctDNA levels while people with malignant melanoma had the lowest. Lower than median ctDNA levels at baseline were associated with better overall survival (adjusted HR 0.49, 95% CI 0.29 to 0.83), progression-free survival (adjusted HR 0.54, 95% CI 0.34 to 0.85) and clinical benefit rate (odds ratio [OR] 3.24, 95% CI 1.19 to 8.8).

At the start of cycle 3 of pembrolizumab, 45% of people (33 of 74) had lower ctDNA levels compared with baseline. Of these, 14 people (42%) had an objective response compared with only 1 (2%) person whose ctDNA level increased from baseline (OR 28.7, 95% CI 3.51 to 253). Change in ctDNA levels was also associated with better clinical benefit rate, overall survival (adjusted HR 0.36, 95% CI 0.18 to 0.71) and progression-free survival (adjusted HR 0.33, 95% CI 0.19 to 0.58). Authors reported that using change in ctDNA along with response evaluation criteria in solid tumours (RECIST) improved risk classification.

Strengths and limitations

The overall sample size was 94 people, with relatively small numbers in each of the 5 cohorts. The authors acknowledged that some cohort analysis was limited by the small sample sizes. Sample sizes also varied across timepoints depending on the number of viable samples available. Samples were collected prospectively but analysis was not done at the same time and did not impact treatment. Some authors were employed by the company.

Christensen et al. (2019)

Study size, design and location

Prospective cohort study in 68 people with localised muscle-invasive bladder cancer in Denmark. Everyone had transurethral resection of bladder tumour (TURBT) followed by neoadjuvant or first-line chemotherapy and cystectomy.

Intervention

Signatera in addition to standard care. Blood samples for ctDNA analysis were collected at scheduled clinical visits and before chemotherapy.

Key outcomes

Recurrence was found in 13 people (20%) with data (n=64). After resection before chemotherapy, 24 people were ctDNA-positive. Of these, 46% (11 of 24) had recurrence during the study compared with 3% of people (1 of 35) who were ctDNA-negative (HR 29.1, p=0.001).

Detecting ctDNA after chemotherapy before cystectomy was also prognostic. At this timepoint, 8 people were ctDNA-positive with a 75% recurrence rate. Comparatively, 55 people were ctDNA-negative with an overall recurrence rate of 11% (6 of 55; HR 12.0, p<0.001). Everyone who tested ctDNA-positive had residual disease or lymph node metastases at cystectomy. Overall, 35 people had no histologically proven residual cancer at cystectomy, of whom all were ctDNA-negative.

After cystectomy, 17 people were ctDNA-positive of whom 76% (13 of 17) had recurrence. No one who was ctDNA-negative at this timepoint (n=47) had recurrence. Multivariable Cox proportional hazards regression analysis found that ctDNA status was the strongest predictor of recurrence-free survival after cystectomy (HR 129.6, p<0.001). ctDNA was found a median of 96 days (range -83 to 245 days) before imaging found metastatic relapse. Serial analysis of ctDNA during surveillance after cystectomy found metastatic relapse with 100% sensitivity and 98% specificity.

Strengths and limitations

This was a prospective study with serial ctDNA analysis throughout treatment. The study

does not report on the use of ctDNA analysis in treatment decisions or its impact on clinical practice. It is unclear if healthcare professionals saw ctDNA results. The company said it provided funding for the testing used in the study, but samples and methods were provided by the collaborators.

Coombes et al. (2019)

Study size, design and location

Prospective multicentre cohort study in 49 adults with breast cancer in the UK. People were recruited after surgery and adjuvant therapy and had no signs of metastatic disease.

Intervention

Signatera in addition to standard care. Samples for ctDNA analysis were collected every 6 months for up to 4 years.

Key outcomes

At the time of interim reporting of results, 18 people had recurrence of disease, of whom 16 (89%) tested ctDNA-positive. Everyone who did not relapse (31 of 49) tested ctDNA-negative with an assay specificity of 100%. Recurrence occurred within 50 months after surgery with ctDNA detected a median of 8.9 months before clinical relapse (range 14 to 721 days). ctDNA was also detected before positive results on CT scans and other standard care tests such as liver function tests and CA 15-3.

Strengths and limitations

This study reports interim results of a UK multicentre study. Target sample size for the main study was 194 assuming a 20% dropout rate and a 20% rate of recurrence in 2 years. Authors reported that serial plasma samples were analysed blinded but no details of this was provided. It is unclear if healthcare professionals and patients were told ctDNA results or if this impacted treatment decisions. Some results were presented across breast cancer subtype, but sample sizes in these groups were very small which limits the certainty of findings. Authors reported that in addition to presence or absence of ctDNA, the levels of ctDNA can be used to track disease burden over time. But this was based on data from 12 people with only 1 person who did not have relapse. Some authors were affiliated with the company.

Reinert et al. (2019)

Study size, design and location

Multicentre cohort study in 130 people with stage 1 to 3 colorectal cancer in Denmark. Samples were collected prospectively. ctDNA analysis was retrospective and not shared with healthcare professionals or patients.

Intervention

Signatera in addition to standard care. Samples for ctDNA analysis were collected before surgery, after surgery, and every 3 months until death, withdrawal from the study or month 36.

Key outcomes

Five people were excluded because they were lost to follow-up or progressed to stage 4 disease. Overall, 24 people (19.2%) had radiologic recurrence. Before surgery, ctDNA was found in 88.5% of samples (108 of 122) while carcinoembryonic antigen (CEA) was found in 43.3% (53 of 122). After surgery before adjuvant therapy, 89.4% of people (84 of 94) tested ctDNA-negative and 10.6% (10 of 94) positive. Recurrence was higher in people who tested ctDNA-positive (70%) compared with ctDNA-negative (11.9%).

Overall, 58 people had adjuvant chemotherapy. Recurrence was found in everyone who tested ctDNA-positive after adjuvant therapy and in 13.7% (7 of 51) who tested negative (HR 17.5, 95% CI 5.4 to 56.5; p<0.001). Serial ctDNA analysis after definitive treatment (n=75) identified recurrence with 88% sensitivity and 98% specificity. In this group, recurrence occurred in 14 of 15 people (93.3%) who tested ctDNA-positive compared with 2 of 60 (3.3%) who tested negative. Comparatively, CEA analysis found recurrence with 69% sensitivity and 64% specificity. ctDNA analysis detected recurrence a mean 8.7 months before CT scan, but this lead time was not found for CEA.

Strengths and limitations

Treatment and follow-up were clearly outlined and followed Danish Colorectal Cancer Group guidelines that were similar to NICE's guideline on colorectal cancer. The study had an overall sample size of 130 people of which 24 had recurrent disease. ctDNA analysis was retrospective and did not impact treatment decisions or clinical outcomes. Length of

follow up varied as did the number of samples analysed at differing timepoints. This made it difficult to interpret changes in ctDNA status across the study. There was also some discrepancy in the reporting of group sizes which affected clarity of the reported findings. Some authors were affiliated with the company.

Sustainability

No environmental sustainability benefits were reported by the company.

Recent and ongoing studies

There are numerous ongoing and future studies on Signatera. For brevity, only a sample of these are listed below. See clinicaltrials.gov for more studies.

- A phase 2 randomised trial for people with refractory metastatic colorectal cancer using ctDNA. ID: NCT04786600. Status: recruiting. Estimated end date: May 2025. Country: US.
- A phase 2 randomised study of tiragolumab plus atezolizumab versus atezolizumab in people with stage 2 melanoma who test ctDNA-positive. ID: NCT05060003. Status: not yet recruiting. Estimated end date: October 2028. Country: US.
- A phase 3 randomised trial of atezolizumab versus placebo in people with high-risk muscle-invasive bladder cancer who are ctDNA-positive after cystectomy (IMvigor011). ID: NCT04660344. Status: recruiting. Estimated end date: November 2027. Country: global.
- A randomised phase 2 trial of ctDNA-guided second line adjuvant therapy for high residual risk stage 2 to 3 hormone receptor positive, HER2 negative breast cancer. ID: NCT04567420. Status: recruiting. Estimated end date: December 2026. Country: US.
- A randomised phase 3 trial of niraparib versus placebo in people with HER2-negative BRCA-mutated or triple-negative breast cancer with molecular disease (ZEST). ID: NCT04915755. Status: recruiting. Estimated end date: August 2029. Country: global.
- BESPOKE study of ctDNA-guided immunotherapy. ID: NCT04761783. Status: recruiting. Indication: colorectal cancer, non-small-cell lung cancer or melanoma. Estimated end date: May 2025. Country: US.

- BESPOKE study of ctDNA-guided therapy in colorectal cancer. ID: NCT04264702. Status: recruiting. Estimated end date: January 2025. Country: US.
- CIRCULATE trials
  - ALTAIR (NCT04457297). Estimated end date: December 2023.
  - GALAXY (UMIN000039205). Estimated end date: March 2030.
  - US (NCT05174169). Estimated end date: March 2030.
  - VEGA (jRCT1031200006). Date of first enrolment: April 2020.
- Phase 2 study of ribociclib plus adjuvant endocrine therapy for ER-positive breast cancer (LEADER). ID: NCT03285412. Status: recruiting. Estimated end date: October 2026. Country: US.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Five experts commented on this briefing. All were familiar with circulating tumour DNA (ctDNA) testing and 3 were familiar with or had used Signatera.

Level of innovation

All experts said that ctDNA technologies are novel, with 3 considering Signatera to be the first in a new class of procedure. Two experts said that Signatera is 1 of several ctDNA technologies being tested across a range of tumour types and clinical scenarios to determine their clinical utility.

Potential patient impact

The experts commented that Signatera has the potential to help with informing the need for adjuvant therapy and measuring treatment response. It may also help with earlier detection of recurrence. This could then prompt investigations to find the site of cancer and to offer treatment if found. But experts cautioned that they would not begin treatment

based on a positive ctDNA test result without any radiological evidence of recurrence because this has not yet been prospectively validated. They advised that this could have a negative psychological impact if a person was told they tested ctDNA-positive but were not treated because of a lack of radiological findings.

One expert noted that if the ctDNA test is negative, a person may be reassured that their tumour has a lower chance of recurrence. But 1 expert cautioned that results from ongoing trials are needed before Signatera can be adopted in the NHS. They advised that without adequate testing and evidence, there is a risk that people could have not enough treatment or too much treatment. Another expert said there are uncertainties in the management of treatment based on test results which could increase patients' anxieties and clinical pressures.

Signatera needs an adequate sample of resected tumour to develop the assay. One expert advised that it is not suitable for small biopsies. Also, if the tumour relapses with different clonal mutations to the primary tumour, recurrence may not be identified. The frequency of this is uncertain and likely low. Non-genotype-informed ctDNA assays have a higher risk of false positives and are less reliable at detecting very low sequence variants. But they can detect evolving variants and allow for tumour heterogeneity.

Potential system impact

The experts advised that Signatera would be used in addition to standard care. Three experts said it could replace elements of standard care if evidence from prospective randomised trials was available. The experts said that using Signatera after surgery could reduce the use of adjuvant therapy in people who test negative. There is evidence that a ctDNA-guided approach to treating stage 2 colon cancer could reduce adjuvant chemotherapy without affecting survival (Tie et al. 2022) but this trial was not on Signatera. Selecting the right population for adjuvant therapy could have cost savings. But another expert noted that it could result in increased healthcare system burden if the frequency of imaging was increased to confirm ctDNA-positive results. Experts advised that detailed cost-effectiveness analysis is needed across different tumour types and clinical settings.

General comments

All experts advised that ctDNA testing is not routinely used in the NHS because of a lack

of funding and a lack of prospective data on its clinical implementation. Signatera is currently used in research or pilots in limited NHS trusts. The experts advised that the evidence on ctDNA testing is strongest in colon cancer but more evidence is needed for other tumour types.

One expert advised that the European Society for Medical Oncology does not recommend molecular residual disease testing in adjuvant or surveillance settings because of a lack of data from prospective trials. There is uncertainty on whether ctDNA testing results in improved clinical decision making and clinical outcomes. All experts said more prospective evidence is needed. Data should be generated for each tumour type to inform the use of Signatera in both testing settings proposed by the company. Experts acknowledged that gaps in the evidence may be answered by ongoing trials

Expert commentators

The following clinicians contributed to this briefing:

- Dr Michael Braun, consultant in medical oncology, The Christie NHS Foundation Trust. Did not declare any interests.
- Dr Konstantinos Kamposioras, medical oncology consultant, The Christie NHS Foundation Trust. Did not declare any interests.
- Professor Sanjay Popat, consultant medical oncologist, Royal Marsden Hospital. Consultant to Guardant Health and doing a pilot evaluation of Signatera tests.
- Mr Baljit Singh, consultant colorectal surgeon, University Hospitals Leicester. Did not declare any interests.
- Dr Elizabeth Smyth, oncology consultant, Cambridge University Hospitals. Has done research with the company and other companies using their circulating tumour DNA assays and is the cancer lead for the East Genomic Medicine Service Alliance.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement for medtech innovation briefings sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-4759-1