

Caris Molecular Intelligence for guiding cancer treatment

Medtech innovation briefing

Published: 20 September 2017

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Summary

- The **technology** described in this briefing is Caris Molecular Intelligence (CMI). It is used to help guide future management of locally advanced or metastatic cancer.
- The **innovative aspects** are that it uses multi-platform molecular profiling to provide a report describing which cancer treatments may have clinical benefit and any relevant, open clinical trials. The profile is based on the molecular characteristics of the patient's tumour, irrespective of its primary site.
- The **intended place in therapy** would be as a tool to help guide treatment decisions for locally advanced or metastatic cancer in people who are fit for further treatment but have exhausted standard (evidence-based) treatment options and for whom no further guidance on therapy exists.
- The **main points from the evidence** summarised in this briefing are from 5 observational studies in Australia and the US including a total of 1,572 adults in secondary and tertiary care centres. Most evidence shows that CMI-guided treatment is associated with better progression-free survival than clinician decisions alone. There is also some evidence that CMI may lead to improved overall survival.
- **Key uncertainties** around the evidence are that there are currently no randomised controlled studies comparing CMI-guided treatment with non-CMI-guided treatment. There is also limited evidence on CMI-guided treatment for site-specific cancers and metastatic cancer of unknown primary origin, and no evidence on its use in children.

- The cost of CMI is £5,800 per test (excluding VAT), which includes the cost of shipping the sample, the full report, and a consultation between the ordering clinician and a member of the company's medical team. The resource impact would be additional costs compared with standard care, including test costs, sample preparation and additional multidisciplinary team meetings. There is no published evidence assessing the cost effectiveness of CMI.

The technology

Caris Molecular Intelligence (CMI, Caris Life Sciences) is a solid tumour biomarker analysis service. It is intended as a tool to aid decision-making and help identify the best treatment plan for each patient. CMI was marketed as Target Now until 2013.

CMI uses a number of tumour profiling techniques to analyse protein, RNA and DNA in the tumour:

- immunohistochemistry, to determine level of protein expression
- in situ hybridisation, to detect deletions and amplifications in a specific set of genes
- RNA sequencing, to identify fusions and rearrangements of 53 genes
- next-generation sequencing to detect DNA mutations in 592 genes, amplifications in 442 genes, total mutational load and microsatellite instability.

The service is updated over time to represent changes in clinical experience and technological feasibility. A full list of the biomarkers analysed by CMI is available on the [company's website](#).

CMI uses a formalin-fixed paraffin embedded (FFPE) biopsy, ideally taken within 6 months of profiling, which is sent (using a Caris specimen shipper kit) to the Caris laboratory in the US for analysis. CMI uses a proprietary algorithm to generate a patient report, which is sent electronically to the clinician within 14 days of receiving the sample and all relevant documents. The patient report comprises:

- A summary of important findings, including lineage-relevant biomarkers and which chemotherapies, immunotherapies, hormone therapies or targeted therapeutics may be effective against the tumour.
- Details of supporting evidence for each therapy and biomarker, grouped by those with potential benefit, lack of benefit or uncertain benefit.
- A list of any ongoing clinical trials that match the patient's biomarker expression profile (using the company's proprietary Clinical Trials Connector service).

- Appendices with full assay results, value information and technical details for each biomarker and technology.

The report is sent to the clinician with a written consultation from a member of the Caris medical team. Caris also offers a telephone call to the clinician to discuss the individual case in the context of treatment history and available treatment options.

Innovations

CMI is done in a centralised laboratory, covering a wider range of molecular testing techniques than may be available in a local laboratory. The results are analysed and summarised in a single report, so the ordering clinician does not need to collate results from multiple tests. The report includes a list of ongoing clinical trials that match the patient's biomarker expression profile, which means that its usefulness will depend on the number of included trials which are open to NHS patients.

If standard treatments in line with existing guidance have failed but the patient is still fit for further therapy, CMI profiling can identify which of the existing chemotherapies may be of benefit for the patient, based on ongoing research. This information may not currently be available to the oncology treatment team and some of these drugs may not have been considered for use in the specific tumour site before. Treatment decisions based on CMI would represent a shift from therapy based on tumour site to a precision medicine approach based on the unique molecular characteristics of a patient's tumour.

Current NHS pathway

People with locally advanced or metastatic cancer may have 1 or more lines of chemotherapy as standard treatment. For example, the NICE guideline on [colorectal cancer](#) includes chemotherapy regimen recommendations for advanced and metastatic disease. Regimens involving oxaliplatin and irinotecan in combination with fluoropyrimidines should be offered as first- and second-line treatments, based on anticipated side effects and patient choice. Other options are raltitrexed for patients who cannot have fluoropyrimidines or folinic acid, and capecitabine and tegafur with uracil.

There is no current guidance or standard NHS pathway for locally advanced or metastatic cancer in people who have exhausted all standard lines of therapy but who remain fit enough for further treatments. Some molecular profiling tests are used currently (for example, FISH or histopathology) for certain cancer types to test whether it is likely that the patient's cancer will respond to a particular chemotherapy drug. In addition, the [100,000 Genomes project](#) (Genomics England) can provide similar sequence data on the tumour and clarify whether certain pathogenic

mutations are germline or somatic. However, this information does not include the association between a detected abnormality in the molecular profile and a treatment recommendation.

The NICE cancer service guideline on [improving supportive and palliative care for adults with cancer](#) states that the final choice of treatment should be guided by patient preference. NICE also has a series of 'improving outcomes' guidelines for site-specific cancers.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to CMI:

- Foundation One (Foundation Medicine)
- OncoDEEP (OncoDNA).

Population, setting and intended user

CMI is designed to be used for people with locally advanced or metastatic cancer in secondary or tertiary care settings who have no other standard care options remaining, but who are fit enough to consider further treatment. It is not indicated for use in de novo treatment planning because it uses a non-site-specific approach to treatment based on molecular profile, rather than exploring the use of standard care regimens by tumour site.

The CMI report would be requested by an oncologist, pathologist or histopathologist, through a requisition form sent to Caris. Pathology laboratory staff would prepare the biopsy sample using standard sample fixation techniques.

Costs

Table 1 Cost of CMI

Product/device	Cost (excluding VAT)	Additional information
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<p>CMI</p>	<p>£5,800, including the full report, a consultation between a member of the Caris medical team and the ordering oncologist, and all sample shipment costs.</p> <p>Caris Life Sciences offers a discount of £775 for prepayment.</p>	<p>There are no additional consumables or maintenance needed to use the product. The only training that would be needed is on preparation of the shipping kit to be sent.</p>
<p>Biopsy (only for patients who have not had a biopsy sample taken within 6 months of CMI being done)</p>	<p>The cost of biopsy varies by cancer type. The weighted cost of all biopsy procedures for cancer patients (excluding biopsy for diagnostic purpose) is calculated as £251 (NHS reference costs 2015/16). This includes direct cost, indirect cost and overhead costs.</p>	

Costs of standard care

Standard care in this indication is determined during multidisciplinary team meetings and based on clinician and patient choice. The weighted cost of a multidisciplinary team meeting for cancer patients is £111 (NHS reference costs 2015/16).

Resource consequences

No published evidence on the resource consequences of adopting CMI was found.

Two specialist commentators estimated that it currently takes 1 to 8 weeks to test for molecular-targeted therapies, depending on the test requested.

Caris returns the CMI report within 14 days of receiving the sample, and it takes 2 to 3 days for a shipment sent from England to arrive at Caris. A specialist commentator estimated that preparing a sample for shipping using an existing FFPE biopsy would take around 30 minutes, but that retrieving a stored biopsy from the local pathology service may take 7 to 10 days. Preparing a newly taken FFPE biopsy for shipping would take 3 to 4 days.

The time taken to prepare the sample, send it and receive the report all need to be taken into account when planning treatment. If the timings are not properly managed, some patients could

start treatment while waiting for the CMI report, which could lead to their treatment needing to change.

A specialist commentator estimated that the total additional time needed for sample preparation and analysis of a CMI report would be around 1 hour per patient.

No additional facilities or technologies would be needed to adopt CMI.

CMI is currently available privately to people who choose to pay or for people enrolled in a CMI clinical trial. It is also currently used for research purposes in approximately 30 NHS hospitals. Some private health insurance companies cover CMI on a case-by-case basis.

Regulatory information

Caris Molecular Intelligence (CMI) was CE marked as an in vitro diagnostic medical device in 2015.

A search of the Medicines and Healthcare products Regulatory Agency website revealed that no manufacturer field safety notices or medical device alerts have been issued for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

People with cancer are protected under the Equality Act from the point of diagnosis.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). 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

This briefing summarises 5 studies including a total of 1,572 patients. Three are published prospective studies (n=168), 1 is a retrospective study from a registry-based cohort (n=224) and 1 is a conference abstract reporting a large prospective study (n=1,180). None of the studies were done in the UK.

Table 2 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

There are a relatively large number of published studies for Caris Molecular Intelligence (CMI), including interventional prospective studies. CMI changes over time to account for new clinical experience and biomarkers, which means that the generalisability of earlier published evidence to the current version of CMI is uncertain.

Many of the trial outcomes were relevant to the NHS, including overall survival, CMI influence on decision-making and progression-free survival ratio (defined as progression-free survival using the CMI-guided therapy compared with progression-free survival using the most recent therapy with which the patient's disease progressed). However, the studies selected for inclusion were from Australia and the US.

Two of the 5 studies evaluated site-specific cancers. Future studies should include additional prospective comparisons of CMI-guided therapy with clinician-led decisions for treating site-specific cancers, to better understand the effect on specific cancer types.

None of the studies were randomised, but this trial design is difficult to implement in this population. There may be ethical concerns with randomising patients to a non-molecular profiling arm, because some clinicians use molecular profiling as part of routine decision-making.

Table 2 Summary of evidence

Dean et al. (2016)	
Study size, design and location	54 patients with heavily pre-treated advanced cancer or with rare tumours in a prospective, single-centre study. Australia.

Intervention and comparator(s)	CMI-guided therapy compared with clinicians' choice alone.
Key outcomes	CMI-guided therapy recommendations differed from clinician recommendations in 89% of the study population. CMI-guided therapy showed clinical benefit (defined as improved quality of life or performance status, symptoms, body weight or response rate based on imaging using RECIST) in 61% of heavily pre-treated tumours, 69% of rare tumours, and 43% patients who had previous standard first-line therapy. 60% of evaluable patients had a PFS ratio of 1.3 or higher.
Strengths and limitations	The study did not use randomisation and each person acted as their own control, so the results could not be compared with the clinician's initial choice of next best therapy. The study included a broad range of tumour types, which limits conclusions for different cancers.
<u>Herzog et al. (2016)</u>	
Study size, design and location	224 patients with advanced stage recurrent epithelial ovarian cancer in a retrospective, registry-based observational multicentre study. Location unclear.
Intervention and comparator(s)	CMI; 2 cohorts were compared based on the matching of treatment to CMI recommendations (n=121, matched cohort) or patients who had at least 1 treatment associated with potential lack of benefit based on CMI (n=103, unmatched cohort).
Key outcomes	The matched cohort had a significantly greater improvement in OS from the time of molecular profiling (median 36 months) compared with the unmatched cohort (median 27 months). Patients who had more than 1 drug in the lack-of-benefit category trended towards worse OS than those who had only 1 drug in this category.
Strengths and limitations	The study did not use randomisation, but it did report that bias was accounted for (statistical analysis not specified) in age, race, stage, histology, grade and site of biopsy. Potential for bias remains in selection bias because of clinicians choosing to profile some patients over others, and choosing whether or not to follow biomarker recommendations based on unrecorded patient characteristics.
<u>Jameson et al. (2014)</u>	

Study size, design and location	28 patients with previously treated metastatic breast cancer in a prospective, multicentre pilot study. US.
Intervention and comparator(s)	CMI-guided therapy compared with clinicians' choice alone.
Key outcomes	<p>Of the 28 patients enrolled, 25 were evaluable. MMP was done on fresh core biopsies and the results were sent to a committee which selected CMI-guided treatment for all. None of the CMI-guided therapies were the same as those the clinician would have chosen.</p> <p>11 patients (44%) had a PFS ratio of 1.3 or higher after treatment and median survival was 10 months. Partial responses were noted in 5 patients, stable disease in 8 and no progression at 4 months in 9.</p> <p>12 patients had a PFS ratio of less than 1.3 and median survival was 4 months; 2 patients had a scan outside of the required time frame and therefore were not considered responders.</p>
Strengths and limitations	The sample size was powered to identify PFS ratio using a type I error rate of 5% and a power of 90%. No investigational agents were included as therapy in this study.
<u>Spetzler et al. (2015)</u>	
Study size, design and location	1,180 patients with a variety of solid tumours in a prospective study. US.
Intervention and comparator(s)	CMI-guided therapy compared with clinicians' choice alone. Cohort 1 (n=510) consisted of patients who had 1 or more drugs predicted to be of benefit and no drugs predicted to lack benefit. Those that had at least 1 drug predicted to lack benefit were placed in cohort 2 (n=500).
Key outcomes	Survival analysis of cohort 1 versus cohort 2 showed a median increase in OS of 274 days (978 versus 704 days). Clinicians indicated (by a self-report questionnaire) that CMI influenced their decision in 58% of cases. Of these, 97% had a drug from the benefit category and 46% did not have any lack-of-benefit category drugs.
Strengths and limitations	This was a published abstract, so detailed methodology is limited. It is unclear how the study determined whether CMI influenced clinician decisions.

<u>Von Hoff et al. (2010)</u>	
Study size, design and location	86 patients with refractory metastatic cancer (mainly breast, colorectal and ovarian; 32 had other, rarer cancers) in a prospective, pilot cohort, multicentre study. US.
Intervention and comparator(s)	CMI-guided therapy compared with clinicians' choice alone.
Key outcomes	In 84 patients with a molecular target detected, 66 (78%) were treated according to CMI results. Of these, 18 (27%) had a PFS ratio of 1.3 or higher and a median survival of approximately 10 months.
Strengths and limitations	The study did not use randomisation and each person acted as their own control. Ascertainment bias may exist with the PFS ratio influenced by frequency of tumour evaluation in the control and evaluation periods. The study was limited by attrition (38 of the original 106 patients who consented were lost to follow-up; 20 withdrew before CMI, mainly because of not wanting additional therapy or worsening condition, and 18 withdrew after having CMI, mainly because of worsening condition and withdrawing consent).
Abbreviations used: CMI, Caris Molecular Intelligence; MMP, multi-omic molecular profiling; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.	

Recent and ongoing studies

- LCC-CARIS-01: A pilot feasibility study to assess the use of molecular profiling to determine choice of treatment for patients with gynaecological cancer. ClinicalTrials.gov identifier: NCT02668913. Status: ongoing, currently recruiting. Indication: epithelial ovarian cancer, peritoneal cancer, fallopian tube cancer, gynaecological malignancy. Device: CMI.
- Caris Molecular Intelligence Registry (CMIR): multi-centre, observational outcomes database designed to collect data on the demographics, presentation, diagnosis, treatment, resource use, quality of life and outcomes of subjects utilising Caris Molecular Intelligence services for treatment of a solid tumour. ClinicalTrials.gov identifier: NCT02678754. Status: ongoing, enrolling by invitation only. Indication: solid tumour cancer. Device: CMI.

- ONCO-T-PROFIL: single-centre feasibility study of molecular profiling in patients with advanced solid tumours refractory to standard treatments. Status: ongoing, completed recruitment. Indication: solid tumour cancer. Device: CMI.

Specialist commentator 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.

Two out of 4 specialist commentators were familiar with Caris Molecular Intelligence (CMI): 1 had used it before and 1 is currently using it.

Level of innovation

One specialist stated that CMI was only a minor variation on the current UK standard of care, but another felt that it represented a paradigm shift in managing cancer. Two specialist commentators stated that the multi-platform nature of CMI and the report's provision of a list of potential drugs to use were both innovative aspects. The commentators were aware of similar technologies, but noted that CMI is the only test that combines immunohistochemistry, in situ hybridisation and next-generation sequencing.

Potential patient impact

All 4 specialist commentators thought that CMI offered potential benefits to patients by guiding the most appropriate therapy, and steering clinicians and patients away from treatments that are predicted to have no benefit.

The specialists identified a range of people who may benefit from CMI, including people:

- with advanced and multi-organ cancers
- with cancer of unknown primary origin and people with malignancy of an unknown origin, for whom using CMI could avoid the need for costly and potentially invasive investigations
- with rare cancers for whom published evidence to guide therapy is unavailable
- who have exhausted standard treatment options
- who may tolerate targeted therapies better if a driver mutation is found

- who are in hospitals or services where current 'best practice' does not occur.

All 4 specialists stated that CMI has the potential to improve clinical outcomes, leading to more diverse treatment pathways and allowing a broader range of therapies and potentially less invasive treatments to be offered.

Potential system impact

The specialist commentators had mixed views on the cost-saving potential of CMI. One felt that it would cost less overall because it would prevent people with advanced cancers and multiple cancers from starting treatments that offered little to no benefit. Two commentators noted that the system impact would only become clear through validation of the technology, and if it could be shown that clinicians were willing to follow CMI's recommendations and modify established patterns of care. Another specialist thought that using CMI was likely to cost more than current standard care, simply because of the cost of the test itself and potentially the costs of appropriate treatments it identified.

One specialist thought that CMI may lead to an increase in outpatient treatment. Another felt that it would shift funding from treatment to diagnosis, but both they and 1 other commentator did not think that there would be a change in how patients were managed, in terms of the setting. Two specialist commentators thought that there may be an increase in cost and resources in terms of taking fresh biopsies, but noted that archived samples can also be used. Two specialists thought that CMI's high cost may prohibit its use in the NHS.

Two specialist commentators thought that some training in the interpretation of the report would be needed, but this is provided by the company. One commentator noted that CMI could potentially recommend drugs that may not be licensed for use in the relevant indication.

General comments

One specialist commentator stated that CMI has sometimes suggested treatments they would not otherwise have considered. Another commentator stated that CMI has limitations, and that not all tests achieved successful molecular profiles (for unknown reasons). They added that CMI was not able to detect all abnormalities known to be present within the tumour that was profiled.

Three specialist commentators felt that more evidence is needed for CMI, including specifically: testing in a UK centre; technical research on multi-platform molecular profiling; cost-effectiveness analyses; trials of CMI-guided therapy compared with clinician choice in cancers of unknown

primary origin and malignancy of unknown origin; and comparisons of current best care with CMI-guided treatment.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Jonathan Krell, consultant oncologist, Imperial College Healthcare NHS Trust. No relevant conflicts of interest.
- Dr Geoff Hall, chief clinical information officer and oncologist, Leeds Teaching Hospitals NHS Trust. Dr Hall has received research funding from Quintiles IMS, Philips Healthcare and Innovate UK. He has been a paid consultant to Astra Zeneca and Quintililes IMS. He has co-authored a British Gynaecological Cancer Society statement on BRCA testing ovarian cancer and was previously an expert on a submission to NICE (Erythropoietin in cancer patients).
- Dr Sara Edward, consultant histopathologist, Leeds Teaching Hospitals NHS Trust. No relevant conflicts of interest.
- Dr Angus McGregor, consultant histopathologist, University Hospitals of Leicester NHS Trust. No relevant conflicts of interest.

Development of this briefing

This briefing was developed for NICE by King's Technology Evaluation Centre. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-2632-9