# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# DIAGNOSTICS ASSESSMENT PROGRAMME

## Early value guidance consultation document

## CaRi-Heart for predicting cardiac risk in suspected coronary artery disease

The National Institute for Health and Care Excellence (NICE) is producing early value assessment guidance on using CaRi-Heart in the NHS in England. The diagnostics advisory committee has considered the evidence and the views of clinical and patient experts. This topic is part of the pilot using the new early value assessment approach. Early value assessment guidance recommendations are conditional while more evidence is collected on the technology to address uncertainty in the evidence base. Once further evidence is collected, this guidance will be reviewed to make a decision on the routine adoption of the technology.

**This document has been prepared for public consultation.** It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the external assessment report).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound, and a suitable basis for guidance to the NHS?

### Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:



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- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

**Note that this document is not NICE's final guidance on CaRi-Heart for predicting cardiac risk in suspected coronary artery disease (CAD). The conditional recommendations in section 1 and the accompanying points on evidence generation in section 4 may change after consultation.**

After consultation, NICE will consider the comments received. The final recommendations will be the basis for NICE's early value guidance on using the technology with evidence generation.

**Key dates:**

Closing date for comments: **31 January 2023**



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# 1 Recommendations

1.1 CaRi-Heart is not recommended for use while further evidence is generated. It should only be used in the context of research to predict cardiac risk in people with suspected coronary artery disease (CAD).

1.2 Further research is recommended (see the section on further research) on:

- clinical outcomes for people with suspected CAD who had CaRi-Heart testing
- how CaRi-Heart results affect clinical decision making compared with UK standard clinical practice
- the costs to the NHS of using CaRi-Heart
- how well CaRi-Heart predicts cardiac risk to validate it in a UK population; in particular, data should be generated in the following subgroups: women, people from different ethnic backgrounds, and people who do not have CAD identified on CT coronary angiography (CTCA).

### Why the committee made these recommendations

There is an unmet clinical need to more accurately identify people who are at increased risk of heart attack or cardiac death. CaRi-Heart assesses the extent of inflammation around the arteries, which a CTCA scan (part of the standard risk assessment) does not. Clinical evidence shows that CaRi-Heart improves cardiac risk prediction compared with using a model based on traditional clinical risk factors. So it could better identify people (with or without CAD) who have coronary inflammation, who may need further treatment to lower their cardiac risk. But how its results might improve outcomes of people with recent-onset chest pain is unclear. This is because CaRi-Heart provides more information than UK standard clinical practice (CTCA alongside clinical assessment of risk factors) so the treatments that



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would be offered based on a CaRi-Heart result are not clearly defined, and there is no data on clinical outcomes after a CaRi-Heart result. It is also uncertain how CaRi-Heart would perform compared with UK standard clinical practice.

CaRi-Heart's cost to the NHS is unknown because the company has not yet specified the price, and no data was identified on the costs or resource use associated with implementing CaRi-Heart. Based on the number of people who could be offered it, the costs to the NHS, if it were implemented while evidence is generated to demonstrate its value, could be substantial.

Because of the uncertainty around its benefits and costs, CaRi-Heart cannot be recommended for routine use in the NHS. But it might more accurately identify people at risk of heart attack or cardiac death than the standard risk assessment alone, so further research is recommended.

# 2 The technology

## The intervention

2.1 CaRi-Heart (Caristo Diagnostics) is a medical imaging analysis software that uses artificial intelligence (AI) to analyse images from CT coronary angiography (CTCA).

## The comparator

2.2 The comparator was CTCA plus clinical assessment of risk factors for cardiovascular disease (CVD), such as hypertension, diabetes, dyslipidaemia, smoking, and a family history of CVD.

## Clinical need

2.3 Coronary artery disease (CAD) affects the arteries that supply blood to the heart muscle. Fatty plaques can build up on the walls of these arteries, narrowing them. This reduces blood flow and can result in angina, stroke and heart attack. Heart attack risk is also linked to inflammation in the wall



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of the artery. This can cause plaque to form and rupture, which can block an artery, leading to acute coronary syndrome or sudden death.

2.4 In current standard practice people with recent-onset chest pain are referred to have a CTCA, which is non-invasive and visualises coronary arteries to identify abnormalities such as plaque build-up and narrowing. But CTCA scans do not identify inflammation around arteries.

2.5 CaRi-Heart can identify inflammation, and its extent, by analysing images from CTCA scans. It aims to identify risk of cardiac mortality with greater discrimination than the currently used clinical risk-factor based models and improve outcomes by personalising prevention and treatment.

# 3 Committee discussion

The diagnostics advisory committee considered evidence on CaRi-Heart for predicting cardiac risk in suspected coronary artery disease (CAD) from several sources, including an early value assessment report and an overview of the report. Full details are in the project documents for this guidance.

## Benefits of the technology

### Risk prediction

3.1 The clinical experts explained that, although CT coronary angiogram (CTCA) can identify abnormalities in coronary arteries, such as plaque build-up and narrowing, it does not identify all people who are at risk of a cardiac event. They said that some people assessed as not having CAD go on to have a heart attack. Improved risk prediction could help to identify these people so that they can be offered treatment to lower their risk.

### Telling patients about cardiac risk

3.2 A patient expert emphasised the importance of clearly communicating a CaRi-Heart result and explained that a ‘high risk’ result could make



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someone anxious. But they said that it may still help people to be better informed about their cardiac risk, provided they have clear information on possible treatments and how to lower their risk. The clinical experts added that having an objective measure of risk could help with explaining how people can reduce their risk. And it may encourage people to take their medication and make lifestyle changes, which could improve outcomes.

### Equity of access to treatment

3.3 The clinical experts said that particular groups, such as women, are often underdiagnosed and may therefore have less access to treatment to reduce their cardiac risk. They explained that an objective measure of risk could improve equity of access if it accounts for factors such as sex, ethnicity and social deprivation, and improves risk prediction.

## Clinical effectiveness

### Benefits of CaRi-Heart from the evidence

3.4 The external assessment group (EAG) found 1 study that assessed the prognostic performance of CaRi-Heart for predicting cardiac death in people with suspected stable coronary disease (Oikonomou et al. 2021). The study was a model development and validation study, which included 3,912 people having CTCA to assess stable coronary disease. The results of the study showed that it was better at predicting risk than a risk model based on traditional clinical risk factors (smoking, hypercholesterolaemia, hypertension, diabetes, Duke index, presence of high-risk plaque features, and epicardial adipose tissue volume). The EAG also found studies that supported a link between coronary inflammation and the risk of adverse cardiac events. The committee agreed that, based on the results of Oikonomou et al. 2021, CaRi-Heart was likely to improve risk prediction for cardiac death.



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## Comparator

3.5 The clinical experts said that the comparator used in the CaRi-Heart study did not reflect UK clinical practice, which limits the generalisability of the study. They said that standard UK practice involves assessing the CTCA image alongside clinical risk factors. Scores such as coronary artery calcium score may be used to guide risk assessment. The clinical experts also said that other risk scores such as QRISK3 may be used if someone has been assessed as not having CAD. One clinical expert said that QRISK3 has been validated in a primary care population, but not in people referred for CTCA for chest pain. But they added that people may be referred back to primary care after a 'no CAD' result. The committee concluded that there was some uncertainty around the extent to which CaRi-Heart might improve risk prediction compared with current UK standard clinical practice. It said that the comparator for future studies should include assessing CTCA images alongside clinical risk factors, and that QRISK3 should be used in the 'no CAD' group.

## External validation

3.6 The EAG suggested that the German dataset used in Oikonomou et al. 2021 to externally validate the CaRi-Heart prediction model had been used in a previous study that may have contributed to developing the algorithm used for CaRi-Heart. So, there was some uncertainty about whether its performance can be reproduced and is generalisable to a new and different population. The company explained that the dataset was only ever used in both studies to validate the algorithm. The EAG noted that the studies did not report enough information to be able to assess this. The clinical experts agreed that the reporting in the 2 studies was unclear, and that their results would have been more robust if they had used different datasets. They also questioned if there were likely to be differences between a German and a UK population. One clinical expert who had used CaRi-Heart said that the variables that are input are mostly



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objective ones. They thought that most would be similar for the 2 populations. But they thought the UK population might be slightly higher risk, and that levels of social deprivation may be different between the 2 countries. The committee concluded that it was uncertain if the dataset used to validate CaRi-Heart was truly external, and that further external validation data would be useful, particularly in a UK setting. The company said that a validation study in the UK is ongoing.

### Important subgroups

3.7 The committee discussed inequity of access to treatments for some groups of people, in particular women. The company said that the Oikonomou study presents some data that suggests the prognostic performance of CaRi-Heart is consistent by subgroups including age, sex, CAD status (obstructive and non-obstructive) and ethnicity. The committee concluded that it would be important to collect this data in any ongoing validation of CaRi-Heart to address equality issues identified during the assessment. It also said that data should be collected to demonstrate prognostic performance in people who do not have CAD identified on CTCA (the 'no CAD' group).

### Impact on risk assessment

3.8 The EAG found no evidence on how CaRi-Heart analysis changes risk assessment or clinical decision making for people with suspected CAD who have a CTCA. The Oikonomou study presented data on how risk groups (low, medium, and high risk) changed when a CaRi-Heart score was used, compared with a clinical risk score. However, the clinical experts said that the clinical risk score used in the study was not used in UK clinical practice. Therefore it was still uncertain how using CaRi-Heart would affect the outcome of a risk assessment compared with CTCA (see section 3.5). The company said that a study was ongoing in the UK and that clinicians in the study were changing their risk assessments after seeing CaRi-Heart reports. They said that other outputs of CaRi-Heart are



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being used alongside the risk score to give a better overall picture of cardiac risk. The committee concluded that how CaRi-Heart influences risk assessment was currently uncertain but that the ongoing study would likely address this.

## Treatment strategies

3.9 The committee discussed the treatments available for people identified with no CAD (low risk), non-obstructive CAD (medium risk) and obstructive CAD (high risk) after a CTCA and how these might change with the introduction of CaRi-Heart. It noted the company's suggestions included starting statins for the low-risk group, increasing the intensity of statins for the medium-risk group, and introducing other anti-inflammatory drugs such as colchicine for the high-risk group. The clinical experts said that colchicine was not licensed or recommended in the UK for this indication. The company pointed out that the latest European Society of Cardiology guidelines suggest low-dose colchicine can be considered for selected high-risk patients. The clinical experts discussed other treatments that may be used more widely in the future, such as PCSK9 inhibitors and inclisiran. But they said that higher quality evidence is needed to show that these treatments could reduce cardiac events and mortality in this population because they were expensive. The clinical experts said that there is good evidence on the effectiveness of starting and intensifying statins, so treatment strategies for people with no CAD or non-obstructive CAD may be clearer. The company said that its ongoing study in the UK, which is part of an NHS artificial intelligence (AI) award, is collecting data on changes in management after a CaRi-Heart result, which may give more insight into how CaRi-Heart affects treatment choices. The committee concluded that further evidence is needed on how CaRi-Heart changes management, and that this may be partially addressed by the ongoing study.



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## Clinical outcomes

3.10 No evidence was found on how CaRi-Heart affects patient outcomes such as cardiac mortality and morbidity. The EAG had found no studies on targeting treatments using any measure of coronary inflammation. It identified evidence that supported the effect of colchicine on reducing cardiac events and some inflammatory markers, but stressed that this did not provide an indication of the efficacy of targeting this treatment using CaRi-Heart or any other measure of coronary inflammation. The committee noted that there was already a lot of evidence showing the effectiveness of statins in reducing cardiac risk. Therefore, people identified as having no CAD on CTCA may have the most potential to benefit from the introduction of CaRi-Heart if they were then offered statins. However, they also said some people having CTCA for chest pain have comorbidities and so may already be on treatments such as statins even if they have no CAD identified on CTCA. For these people it is not clear what further treatments could be offered, and how this would affect their cardiac risk. The committee noted that there is evidence that shows statins may have benefit for all regardless of CAD status. Therefore, if guidance changes in the future to recommend statins more widely then this could affect the extent to which CaRi-Heart can influence treatment options.

The committee discussed how it is likely that a very large study would be needed, with a long follow up, to capture the most important clinical outcome of cardiac death. The clinical experts highlighted that treatments could change during this time, which could mean results were out of date by the time the study reports. The feasibility of a linked evidence approach using the studies identified by the EAG was considered by the committee. It agreed that this approach would be acceptable, but that the studies identified by the EAG were not enough to demonstrate the link between treatments targeted using a measure of coronary inflammation and improved cardiac outcomes. The committee concluded that evidence of a



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reduction in cardiac events or death from a study assessing treatment for people with high and low coronary inflammation was needed.

## Cost and resource use

### Price and population

3.11 No evidence was identified on the costs or cost effectiveness of CaRi-Heart. The company explained that it has not yet specified the price of CaRi-Heart to the NHS but that the price in private practice is £495 per scan. This covers the costs of doing the CaRi-Heart analysis and reporting it, and training clinicians to interpret the report. The clinical experts said that the population eligible for CaRi-Heart if it was implemented with data collection is large, so the cost of using it while data is generated could be substantial.

### Costs and resource use

3.12 The committee heard that there was no evidence on how CaRi-Heart might affect resource use because of changes in treatments or the potential reduction in cardiac events. The EAG said that the University of Oxford was developing an economic model that may address some uncertainties. But it added that there will still be substantial uncertainty because of the lack of evidence around how CaRi-Heart might change treatments and therefore clinical outcomes (see section 3.10). The clinical experts said that treatments such as statins are low cost but if more expensive treatments were offered this could have a much bigger impact on the costs of implementing CaRi-Heart. They said that it would be important to understand the impact of CaRi-Heart on resource use, including primary care follow up appointments and cardiologist time for interpreting and communicating the results of the CaRi-Heart analysis. The clinical experts said that the Oxford model contains implementation costs, but that these were currently unknown. The committee considered the differences between a conceptual model developed by the EAG and



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the University of Oxford model. The clinical experts said that they preferred a lifetime time horizon for the model because the end point was cardiac death. They also preferred people in the model to be stratified by CAD status (no CAD, non-obstructive CAD or obstructive CAD) as well as CaRi-Heart risk as per the EAG conceptual model.

# 4 Recommendations for further research

4.1 Further research is recommended to address the uncertainty around clinical outcomes for people with suspected coronary artery disease (CAD) who have had CaRi-Heart testing. The committee agreed that a linked evidence approach would be acceptable but that the studies identified by the external assessment group (EAG) were not enough to demonstrate the link between treating coronary inflammation and reducing cardiac events or death. It agreed that further studies were needed (see section 3.10). A clinical outcome study using CaRi-Heart to determine treatment strategy with people followed up for long enough to observe a reduction in cardiac events or death would be ideal. Data on subgroups defined by CT coronary angiography (CTCA; no CAD, non-obstructive CAD and obstructive CAD) would also be useful.

4.2 Further data on how CaRi-Heart affects clinical decision making and patient management compared with UK standard clinical practice (CTCA alongside clinical risk assessment) should be collected (see sections 3.8 and 3.9). QRISK3 should be included as a comparator for people who have no CAD identified on CTCA (see section 3.5).

4.3 External validation of CaRi-Heart in a UK setting would be useful (see section 3.6). Research should also include subgroups by sex, age, ethnicity, social deprivation, and CAD status if possible (see section 3.7).

4.4 Data should be collected on the costs associated with using CaRi-Heart, including implementation costs, training costs, and impact on costs and resource use later in the treatment pathway (see section 3.12).



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# 5 Diagnostics advisory committee members and NICE project team

## Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

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