NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Blood-based biomarker tests for surveillance in people at risk of hepatocellular carcinoma
HTG10175

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of blood-based biomarker tests within their indication for surveillance in people at risk of hepatocellular carcinoma.

Background

Hepatocellular carcinoma (HCC) is the most common cancer affecting the liver. It develops from hepatocytes, the main liver cells, and represents up to 90% of primary liver cancer cases. There were a total of 3,021 new diagnoses of HCC in England in 2021. Of these, 2,362 were in men and 659 in women[1].

There are several risk factors for developing HCC, with cirrhosis being the most common one. Approximately 80% to 90% of HCC cases have cirrhosis as a precursor condition[2]. Cirrhosis most commonly arises from chronic liver diseases such as alcohol-related liver disease, hepatitis infection and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)[3]. Less common causes include primary biliary cholangitis, haemochromatosis or α1-antitrypsin deficiency. The remaining 10% to 20% of HCC cases occur in the absence of cirrhosis; these are most frequently associated with chronic hepatitis B infection, which can increase the risk of HCC even without cirrhosis.

The symptoms of HCC include abdominal pain and swelling, loss of appetite, fatigue and jaundice. However, in its early stages HCC is often asymptomatic. Therefore, many cases are diagnosed when the cancer is at a late stage and curative treatment is not an option. The 5-year survival of people with early-stage HCC who receive curative therapy is between 40% and 70%[4]. In contrast, the 5-year survival for late-stage HCC is less than 20% and on average, a person with late-stage HCC would live only about 8 months[4,5]. Late presentation is also associated with poor quality of life and more frequent hospital admissions.

Surveillance for HCC

Because early-stage HCC is often asymptomatic, surveillance in people at risk is recommended in the NHS. The aim is to detect cancer or precancer at a stage when an intervention can be curative.

Recommendations on surveillance for HCC are available in NICE's guidelines on cirrhosis and chronic Hepatitis B and the British Society of Gastroenterology (BSG) guidelines for the management of HCC in adults. These guidelines recommend offering ultrasound with or without measurement of serum alpha-fetoprotein (AFP) every 6 months as surveillance for HCC for people with cirrhosis, as well as for people with Hepatitis B without cirrhosis but with other risk factors. NHS England guidance on a set of minimum standards for HCC surveillance provides a more

detailed list of all people eligible for surveillance in the NHS. This list includes people with:

- Child-Pugh Class A
- Child-Pugh Class B, based on an individual assessment (for example, controlled ascites)
- Child-Pugh Class C with cirrhosis, awaiting liver transplantation
- hepatitis B and significant fibrosis or cirrhosis
- hepatitis B without significant fibrosis or cirrhosis with a family history of HCC
- hepatitis B and hepatitis D coinfection
- hepatitis C and advanced fibrosis
- haemochromatosis and advanced fibrosis
- other liver diseases where the person has a high risk of HCC.

The Child-Pugh score is a scoring system that assesses the prognosis of chronic liver disease, primarily cirrhosis. Based on the score, disease can fall into 1 of 3 classes:

- Class A: Well-compensated liver disease
- Class B: Significant functional impairment (moderately impaired liver function)
- Class C: Decompensated liver disease with poor hepatic function.

The BSG guidelines note that surveillance is not recommended in people who are not fit for cancer-specific therapy, such as those with decompensated cirrhosis who cannot have a liver transplant and those with a very impaired performance status. NHS England guidance on delivering quality ultrasound HCC surveillance says that the appropriateness of ongoing surveillance should be reviewed after each surveillance episode, but there are no formal stopping rules.

If a lesion is detected during ultrasound imaging, the BSG guidelines recommend follow-up imaging with CT or MRI to confirm the presence of HCC (unless the lesion is less than 1 cm, in which case repeat ultrasound in 3 months is recommended).

If a lesion is not detected during ultrasound imaging, but AFP is elevated, the person should also be referred for follow-up imaging with CT or MRI to confirm the presence of HCC. However, there is no guidance on a specific cut-off value for the interpretation of AFP in the NHS. Clinicians use a different cut-off point as well as the change in AFP levels compared with previous measurements to refer for further diagnostic assessment.

In addition to CT or MRI, a biopsy may be needed in some cases. If cancer is detected, the person should be referred using the urgent cancer pathway.

Treatment of HCC

The choice of treatment is dependent on the stage of the cancer, its location and how well the liver function is preserved. Treatment options include interventional procedures such as resection of the tumour, liver transplantation, ablation and transarterial therapies such as chemoembolization or selective internal radiation therapy (SIRT) and systemic therapy.

Radiofrequency ablation, microwave ablation and image-guided percutaneous laser ablation are recommended in NICE's HealthTech guidance on radiofrequency ablation of HCC, microwave ablation of HCC and image-guided percutaneous laser ablation for primary and secondary liver tumours. SIRT is recommended in NICE's

HealthTech guidance on SIRT for primary HCC and NICE's technology appraisal guidance on SIRT for treating HCC. Guidance is also available on liver transplantation and resection procedures, as recommended in NICE's HealthTech guidance on living-donor liver transplantation, radiofrequency-assisted liver resection and laparoscopic liver resection.

Systemic treatment is an option for some people where specific indications are met, as recommended in NICE's technology appraisal guidance on sorafenib, regorafenib, lenvatinib, atezolizumab with bevacizumab, cabozantinib and durvalumab with tremelimumab. People with terminal stage HCC (Child-Pugh Class C) will usually receive best supportive care.

Unmet need

The current approach to surveillance for HCC is suboptimal, because of the low sensitivity of ultrasound to detect early-stage HCC. The quality of ultrasound is also operator dependent, which can affect the likelihood of detecting an abnormality. In addition, the sensitivity of ultrasound is particularly low in certain subgroups, such as people who are overweight or obese. This leads to HCC cases being missed, in particular many early-stage cancers where curative therapy is an option. Currently, less than a fifth of HCC cases are identified at a stage when the person can have curative treatment[5]. In addition, some trusts may have capacity constraints for ultrasound, resulting in surveillance for HCC happening less frequently than every 6 months[6].

Although the addition of AFP improves the overall diagnostic accuracy to detect early-stage HCC, the sensitivity of AFP is particularly low for small tumours; conversely, in some people with chronic liver disease AFP levels can be elevated even in the absence of malignancy[7].

Currently the provision of surveillance for HCC in the NHS is regionally variable and subject to low uptake and adherence. A small number of single-centre retrospective studies show that adherence is between 19% and 76%[8] and many cancers continue to be diagnosed outside of surveillance[5].

These issues are observed in the context of an increasing incidence of HCC and liver disease more broadly.

The technologies

The biomarkers to be appraised are intended to act as an aid in the diagnosis of HCC for people on a surveillance programme:

- protein induced by vitamin K absence or antagonist-II (PIVKA-II)
- lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3).

PIVKA-II is an abnormal variant of the coagulation protein prothrombin. In HCC, serum PIVKA-II levels can often be elevated. PIVKA-II is also known as des-γ-carboxy prothrombin (DCP). AFP-L3 is a specific glycoform (sub-type) of AFP. It is predominantly produced by malignant liver tumour cells. So, as a biomarker, it is strongly associated with HCC.

The results from the technologies can be interpreted as standalone diagnostic results, or can be used within algorithms in combination with clinical information.

For the purpose of surveillance for HCC, the results of the tests or the algorithms can be used in addition to ultrasound. The technologies may also be used as a standalone test without ultrasound. The results of these tests would be used in combination with clinical judgement.

Elecsys PIVKA-II assay and GAAD, a navify algorithm (Roche Diagnostics)

The Elecsys PIVKA-II assay is an immunoassay for the quantitative measurement of PIVKA□II/DCP in human serum or plasma. It is available in both the cobas e and E2G 300 formats. The Elecsys PIVKA-II assay is used with Roche's cobas analyser and has a run time of 18 minutes.

The results of the assay can be used as an additional biomarker alongside AFP or in combination with the Elecsys AFP assay and 2 clinical characteristics (age and gender [biological sex]) as part of GAAD, a navify algorithm. GAAD, a navify algorithm is an in vitro diagnostic multivariate index that combines the quantitative measurement of the 2 biomarkers with the 2 clinical characteristics to produce a risk score between 0 and 10. A score above 2.57 is used to indicate a positive result and increased risk of HCC. GAAD, a navify algorithm is intended as an aid in the diagnosis of early-stage HCC. The calculation formula is not publicly available. An internet-enabled device and access to the Roche navify Algorithm Suite are required. The GAAD score is available instantaneously once all 4 information points are available.

GAAD, a navify algorithm is certified as a general in vitro diagnostic under the In Vitro Diagnostic Directive (IVDD) and has met the Digital Technology Assessment Criteria (DTAC). Elecsys PIVKA-II (both for the cobas e and E2G 300 platforms) is certified as a Class C in vitro diagnostic under the In Vitro Diagnostic Regulation (IVDR). GAAD, a navify algorithm has been trialled in Manchester University NHS Foundation Trust.

Alinity i PIVKA-II and ARCHITECT PIVKA-II assays (Abbott)

The Alinity i PIVKA-II and ARCHITECT PIVKA-II assays are chemiluminescent microparticle immunoassays for the quantitative measurement of PIVKA-II/DCP in human serum or plasma. The Alinity i PIVKA-II assay is used with Abbott's Alinity i analyser and the ARCHITECT PIVKA-II assay is used with Abbott's ARCHITECT i2000SR or related ARCHITECT analysers. The output from the Alinity i PIVKA-II and ARCHITECT PIVKA-II assays is a quantitative measure in mAU/mL, with a range from 3.02 to 3,000,000 mAU/mL and 5.06 to 30,000 mAU/mL, respectively.

The result from the Alinity i PIVKA-II and ARCHITECT PIVKA-II assay can be used as an additional biomarker alongside AFP, or in combination with AFP and clinical characteristics in the ASAP score. The ASAP score is an algorithm that combines the quantitative measurements of AFP and PIVKA-II/DCP with 2 clinical characteristics (age and gender [biological sex]). The equation for calculation is publicly available. The algorithm uses a logistic regression equation to generate a continuous score, with higher values indicating a greater likelihood of HCC. However, a positive ASAP score (defined as a value of above or equal to 0.5256) is used to indicate increased risk of HCC. The ASAP score has been developed for detection of HCC in people with chronic Hepatitis B, but has been validated in broader populations with chronic liver disease, including people with cirrhosis and other underlying liver disease aetiologies.

The Alinity i PIVKA-II and ARCHITECT PIVKA-II assays are certified as Class C in vitro diagnostics under the IVDR. The ASAP score is not a commercial technology and is not CE or UKCA marked.

µTASWako AFP-L3 and µTASWako DCP assays within the µTASWako i30 analyser (Fujifilm)

µTASWako AFP-L3 and µTASWako DCP are immunoassays for the quantitative measurement of AFP-L3 and PIVKA-II/DCP, respectively, in human serum. Both assays are intended for in vitro diagnostic use as an aid in the risk assessment of patients with chronic liver disease for development of HCC. The assays are used with the µTASWako i30 analyser. The µTASWako AFP-L3 assay has 2 outputs – the ratio of AFP-L3 to total AFP and a quantitative measure of total AFP concentration in ng/mL, with a range from 0.3 to 1,000 ng/mL. The output from the µTASWako DCP is a quantitative measure of PIVKA-II/DCP concentration in ng/mL, with a range from 0.1 to 950 ng/mL. The assay preparation time is 10 minutes and the assay run time is 9 minutes.

The results from the µTASWako AFP-L3 and µTASWako DCP assays can be used on their own, or in combination with clinical characteristics in the GALAD score. The GALAD score is an algorithm that combines the quantitative measurements of AFP, AFP-L3 and PIVKA-II/DCP with 2 clinical characteristics (age and gender). The equation for calculation is publicly available. The algorithm uses a logistic regression equation to generate a continuous score, with higher values indicating a greater likelihood of HCC. There is no specified cut-off value to indicate a positive GALAD score.

The µTASWako AFP-L3 and µTASWako DCP assays and the µTASWako i30 analyser are CE-marked but the class is unknown. The GALAD score is not a commercial technology and is not CE or UKCA marked.

Innovative aspects

Some of the technologies combine multiple biomarkers and clinical characteristics. This reduces reliance on a single test and could lead to improved consistency and reduced variability. Those technologies produce results in terms of a risk score, which may be easier to interpret or could allow further risk stratification.

People may have a preference for blood testing over imaging assessment if the blood testing is faster to do and obtain results from, and if it can be done closer to a person's home. So, if the technologies are able to replace ultrasound, there may be benefits in terms of improved adherence to surveillance programmes. This may also improve access to HCC surveillance, if sample collection can be done in community settings. There may also be benefits for radiology services in terms of released capacity.

Interventions	Blood-based biomarker tests for surveillance in people at risk of HCC, including: • Elecsys PIVKA-II assay (Roche Diagnostics) alongside AFP testing • Elecsys PIVKA-II and Elecsys AFP assays within GAAD, a navify algorithm (Roche Diagnostics)

	• Alinity i PIVKA-II assay alongside AFP testing (Abbott) • Alinity i PIVKA-II assay (Abbott) and AFP testing within the ASAP score • ARCHITECT PIVKA-II assay (Abbott) alongside AFP testing • ARCHITECT PIVKA-II assay (Abbott) and AFP testing within the ASAP score • µTASWako AFP-L3 and µTASWako DCP assays with the µTASWako i30 System (Fujifilm) • µTASWako AFP-L3 and µTASWako DCP assays with the µTASWako i30 System (Fujifilm) within the GALAD score. All options listed will be considered in addition to ultrasound and as a replacement of ultrasound.
Populations	People on an HCC surveillance programme.
Subgroups	If the evidence allows, the following subgroups may be considered: • People who are at a particularly high risk of developing HCC such as those with a high aMAP score • People who are overweight or obese • People with alcohol-related liver disease • People with a hepatitis infection.
Comparators	Biannual ultrasound done by a trained healthcare professional with or without measurement of serum alpha-fetoprotein (AFP).
Outcomes	The outcome measures to be considered include: **Intermediate and clinical outcomes** • Diagnostic accuracy • Diagnostic yield/number of newly detected cancers • Stage of newly detected cancers • Test failures or inconclusive tests • Repeat procedures • Number of follow-up investigations received • Time to follow-up investigations • Number and type of treatment received • Time to treatment • Healthcare professional acceptability **Clinical outcomes** • Cancer-related morbidity and mortality • Adverse events **Patient-reported outcomes**

	• Health-related quality of life • Patient acceptability • Adherence to surveillance **Costs and resource use** • Cost of the technology (including the assay and laboratory assessment) • Cost of other surveillance tests • Cost of follow-up investigations and treatments • Training costs • Staff time and cost at different specialisms and levels of pay • Health service use at different settings.
Setting	Secondary and specialist care
Economic analysis	The reference case stipulates that the cost effectiveness of technologies should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. An ongoing NIHR study includes a cost effectiveness analysis with a health economic model developed on the basis of a systematic review.
Other considerations	Guidance will only be issued in accordance with the CE or UKCA marking. Surveillance programmes have potential harms due to false negative and false positive results. False negative tests, or missed cancers, result in harm as a cancer that is present is not identified and treated. False positive tests result in unnecessary downstream investigations, including liver biopsy that can lead to physical and psychological harms. Furthermore, there is the potential for overdiagnosis of HCC. However, incidental findings, such as benign liver lesions or abnormalities in adjacent organs, could be detected on radiological imaging done during surveillance for HCC. This can include both findings on ultrasound and on follow-up investigations such as CT, MRI and biopsy. **Implementation considerations** An increase in positive results can lead to an increase in the workload of radiology services, which are experiencing a shortage in staff and long waiting lists for scans and reviews.

	The NHS England Liver Programme and Cancer Alliances have been working on improving HCC surveillance services in the NHS. This has included improvements to call–recall and patient tracking systems and developing more consistent diagnostic pathways.
Equality considerations	**Condition prevalence and outcomes** Cirrhosis and HCC are more common in older people, men and in Asian and Black ethnic groups. Incidence and mortality rates are also much higher among people who live in deprived areas. This may reflect increased exposure to risk factors in this group, such as alcohol consumption and obesity. This group may also have reduced access to healthcare and lower rates of health literacy. Age, sex and ethnicity are protected characteristics under the Equality Act 2010. People with cancer are also protected under the Equality Act 2010 from the point of diagnosis. **Access to care** There is variation in access to prevention, diagnosis and treatment services for liver disease. **The technology and procedure** Some of the technologies include sex and age as variables in scoring algorithms. This may influence output scores and introduce potential indirect discrimination.
Related NICE recommendations	**Related NICE guidelines:** Cirrhosis in over 16s: assessment and management (2016) NICE guideline NG50. Hepatitis B (chronic): diagnosis and management (2013) NICE guideline CG165. **Related NICE guidance:** Durvalumab with tremelimumab for untreated advanced or unresectable hepatocellular carcinoma (2025) NICE technology appraisal guidance TA1090. Image-guided percutaneous laser ablation for primary and secondary liver tumours (2024) NICE HealthTech guidance HTG722. Cabozantinib for previously treated advanced hepatocellular carcinoma (2022) NICE technology appraisal guidance TA849. Selective internal radiation therapies for treating hepatocellular carcinoma (2021) NICE technology appraisal guidance TA688. Atezolizumab with bevacizumab for treating advanced or unresectable hepatocellular carcinoma (2020) NICE technology appraisal guidance TA666. Regorafenib for previously treated advanced hepatocellular carcinoma (2019) NICE technology appraisal guidance TA555.

	Lenvatinib for untreated advanced hepatocellular carcinoma (2018) NICE technology appraisal guidance TA551. Sorafenib for treating advanced hepatocellular carcinoma (2017) NICE technology appraisal guidance TA474. Living-donor liver transplantation (2015) NICE HealthTech guidance HTG390. Selective internal radiation therapy for primary hepatocellular carcinoma (2013) NICE HealthTech guidance HTG314. Microwave ablation of hepatocellular carcinoma (2007) NICE HealthTech guidance HTG138. Radiofrequency-assisted liver resection (2007) NICE HealthTech guidance HTG136. Laparoscopic liver resection (2005) NICE HealthTech guidance HTG83. Radiofrequency ablation of hepatocellular carcinoma (2003) NICE HealthTech guidance HTG1.

Questions for consultation

General

1. Is the proposed title for this assessment appropriate?
2. Are there any other relevant stakeholders NICE should be aware of?

Care pathway

3. Is the care pathway described appropriately?
4. Are there any other guidelines relevant to the NHS which need to be considered?

Population

5. Is the proposed population described appropriately?
6. Are there any other subgroups that should be included for consideration?
7. Is the aMAP score appropriate for risk stratification to identify people who are at particularly high risk of HCC and who may benefit most from the proposed interventions? Are there any other ways to identify people who are at particularly high risk?

Interventions

8. Are the proposed interventions and use cases described appropriately?
9. Are there any other technologies which need to be included?
10. Should any of the included technologies be excluded and why?

Comparator

11. Is the proposed comparator described appropriately?

Outcomes and costs

12. Are all the outcomes and costs suitable for inclusion in the assessment?

13. Do you consider that the use of the tests can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

Equality and health inequality

14. 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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if, in addition to the equality considerations in the decision problem table, the proposed remit and scope:
    - could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the tests will be used;
    - could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
    - could have any adverse impact on people with a particular disability or disabilities.

      Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

References

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8. Mysco, C. et al. (2025) Health inequalities in hepatocellular carcinoma surveillance, diagnosis, treatment, and survival in the United Kingdom: a scoping review. BJC Reports. 3;13.

