NICE advice

Immunoscore for predicting risk of colon cancer relapse

Medtech innovation briefing
Published: 3 August 2021

www.nice.org.uk/guidance/mib269

Summary

- The **technology** described in this briefing is Immunoscore. It could be used as a risk assessment tool to predict the risk of relapse in people with localised colon cancer.
- The **innovative aspects** are that it uses digital pathology and artificial intelligence (AI)-based algorithms to assess the density of CD3+ and CD8+ T-cells in the tumour and its invasive margins. It represents a novel way of classifying risk of relapse by measuring the person's immune response to the tumour.
- The intended **place in therapy** would be in addition to the tumour, node, metastasis (TNM) classification system in people with stage 2 or 3 colon cancer.

- The **main points from the evidence** summarised in this briefing are from 6 studies, comprising 5 retrospective cohort studies and 1 clinician survey. The evidence base includes over 4,000 people with stage 1 to 3 colon cancer. It shows that Immunoscore, when used with the TNM classification system, is a predictor for time to recurrence, disease-free survival and overall survival. It can also help predict chemotherapy response in people with stage 3 colon cancer having oxaliplatin with 5-fluorouracil and folinic acid (FOLFOX) therapy.
- **Key uncertainties** around the evidence or technology are that none of the published studies included people having treatment in the NHS and the technology's ability to predict chemotherapy response has been shown in people mainly having treatment with FOLFOX.
- The **cost** of Immunoscore is £2,250 per test (VAT exempt).

The technology

Immunoscore (HalioDx) is an in vitro diagnostic test designed to predict the risk of relapse in people with localised colon cancer. The technology is designed to assess the microenvironment surrounding tumour cells, providing a measurement of the person's immune response at the tumour site.

The technology uses image analysis and software to measure the density of specific immune cells (CD3+ and CD8+ T lymphocytes) in digital images of tumour samples from resection surgery. Data have shown that assessing immune status with a scoring system that quantifies the density of these specific immune cells in the core and invasive margins of the tumour can indicate tumour recurrence and survival beyond microsatellite-instability staging (see Mlecnik et al. 2016). The software uses computer vision and neural network-based algorithms to distinguish the tumour zone from healthy tissue before measuring the density of CD3+ and CD8+ tumour-infiltrating lymphocytes at both the core and periphery (or invasive margins) of the tumour and automatically assigning an Immunoscore. There are 5 Immunoscore values (IS 0 to 4). A high Immunoscore of 2 to 4 indicates a higher level of immune cell infiltration, suggesting that the person's immune system is actively fighting the cancer and the risk of relapse is low. A low Immunoscore of 0 or 1 indicates a higher risk of relapse. The technology is intended to be used with the tumour, node, metastasis (TNM) cancer staging system to help guide treatment strategies. This could potentially lead to fewer people having more, or less, chemotherapy treatment than is needed.

The Immunoscore test is done at dedicated HalioDx laboratories (France and the US) using tumour samples in the form of a formalin-fixed paraffin-embedded (FFPE) block or microscope slides. HalioDx organises shipment of the unstained tumour sample to the laboratory using a specimen collection kit containing a prepaid courier company airway bill and test request form. In the HalioDx laboratory, the tumour FFPE block or slides are stained for CD3+ and CD8+ T lymphocytes using an Immunoscore CE-IVD-marked kit and digitally scanned and analysed by the Immunoscore software. Results are reported back to the referring clinician through the HalioDx secure web platform within 10 working days of receiving tumour samples. The company states that the maximum turnaround time of 10 days is guaranteed by standardisation of the process and has been validated by a feasibility study (see Belaloui et al. 2018). The results give the Immunoscore category and risk group. They also give an overview of a clinical management decision tree based on the risk profile. Images are not provided with the test report but the company states that they can be made available on request.

Innovations

Immunoscore uses a novel approach to predict risk of relapse in people with early-stage colon cancer by measuring the person's immune response to the tumour instead of tumour cell biology. It is a tissue-based immune assay, which uses digital pathology alongside deep learning-based algorithms (a type of artificial intelligence) to assess the infiltration of CD3+ and CD8+ T-cells in the tumour core and at the invasive margin. It is the first commercially available tool to do this. It is a non-invasive test that uses already available resection tumour samples, meaning people will not need to have further procedures.

Current care pathway

The main treatments for localised colon cancer are surgery and chemotherapy. The treatment offered depends on the stage and grade of cancer, as well as the general health and fitness of the person having the treatment. The TNM staging system is the most widely used histological classification system for staging cancer.

Standard care for localised colon cancer is to offer surgery to people who are able to have it, to remove the section of the colon containing the cancer. Some people may be offered chemotherapy before surgery.

Adjuvant chemotherapy is recommended after surgery in people with stage 3 colon cancer

to reduce the risk of the cancer returning (relapse). Current standard care for this is capecitabine with oxaliplatin (CAPOX) for 3 months. If this is not suitable, oxaliplatin with 5-fluorouracil and folinic acid (FOLFOX) for 3 to 6 months or single-agent fluoropyrimidine (for example, capecitabine) for 6 months may be an option. The type and duration of chemotherapy treatment is based on the stage and characteristics of the cancer, and the person's performance status, comorbidities, age and personal preferences. Adjuvant chemotherapy is not recommended for routine treatment of stage 1 or 2 colon cancer but may be considered in people with stage 2 disease who have a higher risk of relapse.

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

- NICE's guideline on colorectal cancer.
- European Society for Medical Oncology (ESMO) clinical practice guidelines on diagnosis, treatment and follow-up for localised colon cancer. These state that Immunoscore can be considered in addition to TNM scoring to refine the prognosis of people with early colon cancer and help adjust the chemotherapy decision-making process in people with stage 2 and low-risk stage 3 disease. However, its role in predicting chemotherapy benefit is uncertain.

Population, setting and intended user

Immunoscore is intended to be used for risk classification in people with localised colon cancer (stage 1 to 3) in addition to TNM classification.

Colorectal cancer (cancer of the colon or rectum, or bowel cancer) is the fourth most common cancer in the UK, with around 42,300 new cases diagnosed each year (Cancer Research UK, 2017). Risk factors include increasing age, genetics and family history (particularly syndromes such as familial adenomatous polyposis and Lynch syndrome), inflammatory bowel disease, and other dietary and lifestyle factors. Survival rates have improved over time, and almost 60% of people diagnosed with colorectal cancer live for at least 5 years. Survival is linked to disease stage at presentation, with better survival the earlier the disease is detected and treated.

The technology would be used in secondary care by healthcare professionals, such as medical oncologists involved in making decisions about a person's treatment.

Costs

Technology costs

The company states that the cost per Immunoscore test is £2,250 (VAT exempt). This includes costs associated with ordering and shipping the sample to HalioDx laboratories, as well as the costs associated with processing the sample, running the assay and reporting the Immunoscore test results.

Costs of standard care

Immunoscore is intended to be used in addition to standard TNM risk classification for the staging of localised colon cancer.

Resource consequences

Immunoscore is not currently used in the NHS but has been used by private hospitals in the UK. Adopting Immunoscore is likely to present an additional cost to standard care. However, using the test to refine cancer staging has the potential to be resource releasing if it can help identify people with low risk of relapse who would benefit from more intense surveillance instead of chemotherapy, which is costly and associated with toxicity. Minimal to no training is needed for healthcare professionals using the test, and no changes to facilities or infrastructure are needed to adopt the technology because the test is done at HalioDx laboratories. The test is also done using available resected tumour samples without the need for additional test-specific procedures.

Regulatory information

Immunoscore is CE marked as an In Vitro Diagnostic Medical Device (IVD; other IVD – not listed in Annex II) under Directive 98/79/EC. The test is currently available in the UK as a full service.

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.

The risk of colon cancer increases with age and most colon cancers occur in people over 50 years. Age is a protected characteristic. People with cancer are protected under the Equality Act 2010 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 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 5 retrospective cohort studies and a clinician survey. The evidence base includes over 4,000 people with stage 1 to 3 colon cancer.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

Evidence suggests that Immunoscore could be used to refine prognosis in people with localised colon cancer when used with the tumour, node, metastasis (TNM) classification system, and could help aid chemotherapy decision making.

Immunoscore was assessed in an international retrospective cohort study, which included over 2,600 people with stage 1 to 3 colon cancer (see Pagès et al. 2018). The results showed that Immunoscore significantly predicted time to recurrence (TTR), disease-free survival (DFS) and overall survival (OS). In people with stage 2 colon cancer, it also predicted who was at high and low risk of relapse. Mlecnik et al. (2020) included people with stage 3 colon cancer from 2 cohorts of the Society for Immunotherapy of Cancer (SITC)-led study reported by Pagès et al. (2018). It showed that a high Immunoscore was significantly associated with a prolonged TTR, DFS and OS. Immunoscore also predicted

outcome in people with microsatellite stable (MSS) status, as well as in people with high-risk (T4 or N2) and low-risk (T1 to T3, N1) stage 3 disease.

Two large retrospective studies that used data from independent randomised phase 3 clinical trials in people with stage 3 colon cancer further validated the clinical utility of the test. This included 1,062 samples (after quality controls) from the IDEA France trial that compared the benefits of 3- and 6-month oxaliplatin with 5-fluorouracil and folinic acid (FOLFOX) therapy (see Pagès et al. 2020), and 559 samples from the FOLFOX arm of the NCCTG N0147 trial (see Sinicrope et al. 2020). Results from these 2 studies showed that Immunoscore was strongly prognostic for DFS in people with stage 3 colon cancer.

In addition to predicting prognostic value, 2 studies also reported on the test's predictive value for chemotherapy response in people with stage 3 colon cancer (Pagès et al. 2020 and Mlecnik et al. 2020). The IDEA France study showed that people with a high Immunoscore significantly benefitted from 6-month FOLFOX therapy compared with 3-month therapy, whereas no significant benefit was observed in people with a low Immunoscore. These results were independent of the clinical stage (high risk [T4 or N2, or both] or low risk [T1 to 3, N1]). Mlecnik et al. (2020) included people with untreated disease and people having heterogenous treatments (fluorouracil [5-FU], FOLFOX, capecitabine with oxaliplatin (CAPOX) or folinic acid, fluorouracil and irinotecan [FOLFIRI]). Results showed that the cancer in people with a high Immunoscore responded to chemotherapy and had prolonged survival compared with those whose disease was untreated. People with a low Immunoscore did not benefit from chemotherapy treatment and had statistically similar outcomes to those who did not have chemotherapy.

Evidence suggests that Immunoscore could potentially be used to inform decisions on offering chemotherapy to treat high-risk stage 2 cancer and to inform the duration of adjuvant chemotherapy for treating stage 3 cancer. Data suggest that use of Immunoscore may reduce adjuvant chemotherapy treatment in 70% of people with high-risk stage 2 disease (see Galon et al. 2019) and reduce FOLFOX therapy from 6 to 3 months in 46% of people with stage 3 disease (see Pagès et al. 2020). The generalisability of results to the NHS is limited because none of the published evidence on Immunoscore includes UK centres. Also, the clinical utility of the test in the NHS for optimising chemotherapy duration for stage 3 cancer is unclear. This is because standard care is 3-month CAPOX therapy, and not a choice of 3- or 6-month FOLFOX therapy, which was offered to most people (90%) in the IDEA France study (Pagès et al. 2020). Prospective studies in the UK and including people having treatment with CAPOX would be helpful.

Pagès et al. (2018)

Study size, design and location

Retrospective clinical validity study assessing the prognostic value of Immunoscore in 2,681 people with stage 1 to 3 colon cancer, in 14 centres across 13 countries in Europe (including Belgium, Sweden, France, Germany, the Netherlands, Czech Republic, Italy, Switzerland), North America and Asia.

Intervention and comparator

Immunoscore (high compared with low), no comparator.

Key outcomes

The Immunoscore test showed a high level of reproducibility between observers and centres (r=0.97 for colon tumour; r=0.97 for invasive margin; p<0.0001). In the training set (n=700), people with a high Immunoscore had the lowest risk of recurrence at 5 years. Recurrence rates at 5 years were 8%, 19% and 32% for people with high, intermediate and low Immunoscore respectively (hazard ratio [HR] for high compared with low Immunoscore was 0.20; p<0.0001). Findings were confirmed in the internal (n=636) and external (n=1,345) validation sets. The association between Immunoscore and TTR was independent of a person's age, sex, T stage, N stage, microsatellite-instability status and existing prognostic factors (p<0.0001). Of the 1,434 people with stage 2 cancer, a high Immunoscore was associated with the lowest risk of recurrence and the highest DFS and OS. The difference in risk of recurrence at 5 years was significant (HR for high versus low Immunoscore was 0.33; p<0.0001), even when adjusting for potential confounders in a Cox multivariable analysis (p<0.0001). Immunoscore had the highest relative contribution to survival and risk of recurrence compared with all the other clinical parameters, including the TNM classification system.

There are also published conference abstracts presenting data from various subgroup analyses of this study, including:

- people with stage 1 colon cancer (Galon et al. 2019a)
- people with stage 2 colon cancer with high-risk clinico-pathological features for whom adjuvant treatment may be avoided (Galon et al. 2019b)

- people with T4N0 stage 2 colon cancer (Galon et al. 2020a)
- people with stage 1 to 3 colon cancer from the Asian centres of the study (Galon et al. 2020b).

Strengths and limitations

This was a large international multicentre study that included a training data set (n=700) and internal validation data set (n=636) using samples from centres across Switzerland, Germany, France, US, Czech Republic and Canada. The demographic and clinical characteristics of the patients were well balanced between the training set and internal validation set. Study pathologists and immunologists used standardised operating procedures and staining quality and intensity was validated to ensure consistency among samples. The statistical analyses were done by an independent external group.

People who had preoperative treatment were excluded and adjuvant chemotherapy use was not considered in the study. The study did not include any centres from the UK which may limit generalisability to the NHS. One of the authors is a co-founder of the company.

Pagès et al. (2020)

Study size, design and location

Retrospective clinical validity study of data from a phase 3 randomised trial of 1,322 people with stage 3 colon cancer who were having oxaliplatin-based treatment in France. This study was an ancillary biomarker analysis of the IDEA France Study.

Intervention and comparator

Immunoscore (low compared with intermediate or high scores), no comparator.

Key outcomes

In total, 1,322 people (66%) from the overall IDEA France study's modified intention-to-treat population with available samples were included in the analysis. Overall, 1,062 (85.6%) samples reached the quality control; 43.6%, 47.0% and 9.4% of people in this analysis had low, intermediate and high Immunoscores respectively. A low Immunoscore was associated with a higher risk of relapse or death compared with an intermediate or

high Immunoscore (low compared with intermediate or high score; HR=1.54; p<0.0001). The 3-year DFS was 66.8% for people with a low Immunoscore and 77.1% for people with an intermediate or high Immunoscore. Immunoscore remained significantly independently associated with DFS (p=0.003) when adjusted for sex, histological grade, T or N stage and microsatellite instability. For people having treatment with FOLFOX (92% of people in the study), Immunoscore showed statistically significant predictive value for treatment duration (3 compared with 6 months) in terms of DFS (p=0.057). People with intermediate or high Immunoscore significantly benefitted from 6 months of FOLFOX therapy compared with 3 months (HR=0.53; p=0.0004), including people with clinically low- and high-risk stage 3 colon cancer (all p<0.001). People with low Immunoscore did not significantly benefit from 6-month FOLFOX therapy compared with 3-month treatment (HR=0.84; p=0.27).

Strengths and limitations

The study used data from a large multicentre, randomised trial in 129 centres. The Immunoscore test was done blinded to clinical data. Baseline clinical and histopathological characteristics and the Immunoscore categorisations were well balanced among people having 3 and 6 months of FOLFOX therapy.

Most of the people (90%) in the trial had treatment with FOLFOX so no conclusions can be made about people having CAPOX. The median follow up was 4.3 years, meaning the longer-term treatment benefit of using Immunoscore could not be determined. The study was done in France which may limit generalisability to the NHS. One of the authors is the co-founder of the company and 2 authors are employees of the company.

Sinicrope et al. (2020)

Study size, design and location

Retrospective clinical validity study of data from an international multicentre phase 3 randomised trial in 559 people with stage 3 colon cancer who had treatment with adjuvant FOLFOX. Data from the FOLFOX arm of the phase 3 randomised North Central Cancer Treatment Group (NCCTG) N0147 trial were used to construct Cox models for predicting DFS. The NCCTG N0147 trial included centres from the US, Canada and Puerto Rico.

Intervention and comparator

Immunoscore (low compared with high score), no comparator.

Key outcomes

A low Immunoscore was significantly associated with a shorter DFS (adjusted HR=1.69; p=0.001) after adjusting for age, tumour location, T and N stage, BRAF and KRAS gene mutations, and mismatch repair status. The 3-year DFS for people with a low Immunoscore was 66.6% compared with 82.6% for those with a high Immunoscore. In terms of the relative contributions of variables to DFS risk, the number of positive lymph nodes had the largest impact (43.1%), followed by T stage (18%), BRAF and KRAS status (16.1%) and then Immunoscore (14.9%). Among people in the low-risk group (people with T1 to T3 N1 tumours; n=296), Immunoscore was the strongest predictor of DFS and the only variable to remain statistically significant (HR=0.87; p=0.02).

Strengths and limitations

This study included people with uniform cancer stage and treatment. Data came from a multicentre randomised phase 3 clinical trial, reducing risk of selection bias. The study used a multivariable Cox model to adjust for confounding variables.

The trial did not include UK centres which may limit generalisability to the NHS. Everyone in the trial received adjuvant chemotherapy so the ability of Immunoscore to predict chemotherapy response could not be determined. Two of the authors are co-founders of the company.

Mlecnik et al. (2020)

Study size, design and location

Multicentre, retrospective cohort study evaluating the prognostic value of Immunoscore in 763 people with stage 3 colon cancer. It included people from 2 cohorts (cohort 1, North America; cohort 2, Europe and Asia) of the SITC-led study reported by Pagès et al. (2018).

Intervention and comparator

Immunoscore (high compared with low scores), no comparator.

Key outcomes

Recurrence-free rates at 3 years were 56.9%, 65.9% and 76.4% in people with low, intermediate and high Immunoscores respectively (HR [high compared with low], 0.48; p=0.0003). High Immunoscore was significantly associated with prolonged TTR, OS and DFS (all p<0.001). A statistically significant association between a high Immunoscore and prolonged TTR was also shown in people with MSS status (HR [high compared with low], 0.36; p=0.0003). Immunoscore had the strongest contribution for influencing survival (TTR and OS). Chemotherapy was significantly associated with survival in people with a high Immunoscore with either low-risk cancer (T1 to 3, N1; HR [chemotherapy compared with no chemotherapy] 0.42; p=0.0011) or high-risk cancer (T4 or N2, or both; HR [chemotherapy compared with no chemotherapy] 0.50; p=0.0015).

Strengths and limitations

This was an international study that included data from 14 centres across 13 countries. The ability of Immunoscore to predict response to chemotherapy demonstrated in this study supports IDEA France study findings (see Pagès et al. 2020). Biomarker quality control was blinded to clinical data, and clinical data quality control was blinded to biomarker data. Immunoscore categories were previously defined independently of clinical data. The study used multivariable Cox models stratified by centre and adjusted for potential confounders.

The study population was heterogenous in terms of treatment and follow up but is reflective of real-world practice. People having neoadjuvant treatment were not included. Only 65% and 16% of people in the study had microsatellite instability and mutational status respectively. The study did not include any centres from the UK, which may limit generalisability to the NHS. Authors had financial interests in the company.

Marliot et al. (2020)

Study size, design and location

Retrospective cohort study of 595 people with stage 1 to 3 colon cancer to assess the prognostic value of Immunoscore. Samples from 595 people with stage 1 to 3 colon cancer taken from 3 different studies (see Pagès et al. 2018, ImmuCol and ImmuCol2) were analysed. The interlaboratory reproducibility of Immunoscore was assessed using a second cohort of 100 people with stage 1 to 3 colon cancer treated in Romania. The

analytical precision outcomes were determined using 13 anonymous FFPE colon cancer blocks.

Intervention and comparator

Immunoscore, no comparator.

Key outcomes

Manual and automatic counts for CD3+ and CD8+ T cells were strongly correlated (r=0.94, p<0.001, and r=0.92, p<0.001 respectively). The intensity of the histological staining was not affected by the age of the tumour sample block over a period of 30 years. Immunoscore was not affected by the tumour block selected or the position of the tested tissue section within the tumour block. Consistency of Immunoscores between selected or randomised tumour tissue blocks was 93% and between distant tissue sections from the same block was 95%. Interlaboratory reproducibility was assessed between 2 centres and was shown to have 93% agreement in Immunoscores. Reproducibility of the test was also unaffected by other variables such as antibody lots, staining kits, immunohistochemistry automators and operators. The prognostic validity of Immunoscore was assessed in a cohort of 229 people with stage 1 to 3 colon cancer. The relative proportion of variance for TTR explained by Immunoscore was 53%. This was greater than other prognostic factors included in the model including T stage, microsatellite-instability status and total number of lymph nodes.

Strengths and limitations

Data used to assess the prognostic value of the Immunoscore came from 3 previously published studies, 2 of which were prospective in design. The study tested for multiple variables of sample preparation including lot-to-lot variability of primary antibodies, the choice of tumour block, the reproducibility of the sectioning process, and age and storage of the paraffin block.

Retrospective data used to assess prognostic value of the Immunoscore came from French cohorts only, limiting generalisability to the NHS. Only 1 of the 2 test centres did immunostaining of CD3+ and CD8+ T cells using the CE-marked HalioDX Immunoscore Kit and quantification of cells using the Immunoscore Analyser. Two of the study authors are co-founders of the company.

Barzi et al. (2020)

Study size, design and location

Clinician survey on 10 people with stage 2 colon cancer, in the US.

Intervention and comparator

There were 25 medical oncologists who were presented with 10 patient cases and asked for their recommendations (adjuvant chemotherapy and frequency of surveillance) through an online survey. At a live event, clinicians were presented with Immunoscore data and asked to complete the same patient survey.

Key outcomes

On average, clinicians chose to change their chemotherapy or surveillance recommendations, or both, in 56% of cases. All but 1 clinician (96%) changed their recommendations for at least 1 case, whereas 92% (23/25) changed their preference for chemotherapy in at least 1 case. The rate of change for chemotherapy prescription was 36% per patient case (range: 7 to 13 changes). Surveillance strategies were rarely altered when chemotherapy recommendations changed.

Strengths and limitations

The study was sponsored by the company. The surveys were completed using different formats (online survey versus live event), which may have influenced physician decisions. Also, the study was available as abstract only with limited methodological information such as the time between completing each survey, as well as the level of expertise of the medical oncologists enrolled.

Sustainability

The company claims the technology can potentially reduce unnecessary use of adjuvant chemotherapy and surveillance testing.

Recent and ongoing studies

- Prognostic value of the Immunoscore colon test for disease free survival stratification in stage 3 patients under oxaliplatin treatment. ClinicalTrials.gov identifier: NCT03422601. Status: active, not recruiting. Indication: colorectal cancer and stage 3 colon cancer. Device: Immunoscore. Estimated completion date: July 2019. Country: France.
- Immunoscore as decision guidance for adjuvant chemotherapy in colon cancer (iMAGINE). ClinicalTrials.gov identifier: NCT04488159. Status: not yet recruiting. Indication: colon cancer. Device: Immunoscore. Estimated primary completion date: December 2023. Country: Austria.
- Adjuvant chemotherapy in high-risk stage 2 colon cancer. ClinicalTrials.gov identifier: NCT04303429. Status: not yet recruiting. Indication: high-risk stage 2 colon cancer. Technologies: FOLFOX, XELOX and capecitabine. Estimated primary completion date: January 2022. Country: China.

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.

All 3 experts were familiar with the technology but only 1 had used the technology in clinical practice.

Level of innovation

All experts agreed that the technology is novel. Two experts noted that T-cell infiltration is a known phenomenon and can be assessed by pathologists. The innovative aspect of Immunoscore is that it uses digital technology to quantify T-cell infiltration, which experts believe could provide more reproducible assessments. All experts agreed that the technology would be used in addition to standard care staging (tumour, node, metastasis; TNM) to assess risk of relapse.

Potential patient impact

The main patient benefit identified by the experts is improved patient selection for adjuvant chemotherapy. Two experts noted that this may help people with a low risk of recurrence to avoid having chemotherapy. Another expert said that use of the technology could strengthen the rationale for some people with stage 3 colon cancer only having 3 months of adjuvant chemotherapy. People with stage 2 or 3 resected colon cancer were identified by 1 of the experts as people most likely to benefit from the technology. Another expert did not believe the technology has a role in people with stage 1 or 3 cancer but could be used to better define prognosis and inform chemotherapy decisions in people with stage 2 cancer. The expert noted, however, that chemotherapy is only offered to a small number of people with stage 2 colon cancer who have high-risk features, are fit for chemotherapy and who are often under 70. The remaining expert said the population of people who would benefit is unclear. They also highlighted that stage 2 colon cancer is normally not treated with chemotherapy unless it has very high-risk features.

Potential system impact

One expert said that the technology could lead to fewer hospital visits and fewer chemotherapy side effects, because less chemotherapy would be offered. Another expert said that it is unclear how much additional value using the test would give in addition to standard care in people with stage 2 cancer. Another expert did not think that Immunoscore has the potential to change the current pathway or clinical outcomes to benefit the healthcare system at present. When asked about the cost consequences of adopting the technology, 1 expert thought that it would be cost saving because less chemotherapy would be offered in the adjuvant setting, whereas 2 said it would be more costly than standard care. One expert noted that it is highly unlikely that the technology would result in substantial cost savings through the avoidance of chemotherapy. This is because of the low cost of chemotherapy for stage 2 colon cancer, as well as the high cost of the test and the potentially large numbers of people who may need testing. The expert noted, however, that the number needed to test and the proportion of people where the test would alter treatment is unclear.

General comments

Experts noted that the technology is not currently widely used in the NHS but has been used in the private healthcare setting in the UK. Two of the experts thought adopting the

technology would be more resource intensive; 1 expert noted that some infrastructure would be needed to prepare and send samples for testing. The experts said training to use Immunoscore was minimal or not required and no additional facilities were needed. Potential issues preventing adoption were identified as costs, uncertainty regarding benefits and the adoption of measuring circulating tumour DNA as an alternative. In terms of safety, no adverse effects were anticipated because the test is non-invasive and done on tumour samples. One expert noted a potential risk of the tumour sample being lost during transportation to the testing laboratory. Two of the experts had no concerns regarding the safety and efficacy of the technology. One expert did not think its clinical and cost effectiveness has been sufficiently shown in people with stage 2 colorectal cancer having treatment in the NHS. The expert noted that additional UK-based prospective evidence is needed. This should compare the technology with high-quality pathology reporting (as set out in the Royal College of Pathologists' minimum dataset for histopathological reporting of colorectal cancer, which includes TNM staging as well as other prognostic factors) to define effectiveness and the number needed to test to affect decision making.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Michael Braun, consultant in medical oncology, Christie NHS Foundation Trust, did not declare any interests.
- Rob Glynne-Jones, consultant clinical oncologist, Mount Vernon Cancer Centre, did not declare any interests.
- Dr Tony Dhillon, consultant medical oncologist, Royal Surrey Hospital, presented Immunoscore at a HalioDx-sponsored conference in Hong Kong, China in May 2021.

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: 978-1-4731-4215-2