NICE advice

# LiMAx system for assessing the functional capacity of the liver

Medtech innovation briefing
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## Summary

- The **technology** described in this briefing is the LiMAx liver function capacity test. It is intended to predict post-operative outcomes in people who are being considered for liver surgery or liver transplant, to allow individualised management mainly by informing the surgeon on the extent of resectability.
- The **innovative aspects** are that it offers point-of-care measurement of a novel marker of liver function.
- The intended **place in therapy** would be as well as standard tests and investigations in people being considered for liver surgery or transplant.
- The **main points from the evidence** summarised in this briefing are from 6 studies (1 randomised control trial and 5 observational studies) including over 1,700 adults with primary or secondary liver tumours having liver surgery and 266 liver transplant candidates. They show that LiMAx is useful for preoperative risk stratification and can help predict the likelihood of post-operative liver failure and mortality risk before surgery.

- **Key uncertainties** around the evidence or technology are how generalisable the results are to NHS practice because all available evidence is from the German healthcare system, and most are from 1 centre. There is less evidence on its use in liver transplants.
- The **cost** of each LiMAx test is £341 (excluding VAT) assuming a minimum annual usage of 50 tests. The **resource impact** would be an additional cost to current practice. If the test were to accurately predict post-operative outcomes, there could be savings from reductions in post-operative complications and reduced length of stay.

# The technology

LiMAx (Humedics GmbH) is a point-of-care diagnostic test for the quantitative measurement of the ratio of breath levels of $^{13}CO_2$ to $^{12}CO_2$. This can be used as a measure of functional liver capacity in people with primary and secondary liver tumours, as well as in people having liver surgery or liver transplant. The test is designed to be used with other investigations to help predict and monitor post-operative outcome in liver resection and transplant. The technology helps in selecting patients who are likely to benefit from liver resection. It has the potential to improve patient outcomes by allowing individualised treatment strategies, mainly by informing the surgeon on the extent of resectability.

The technology comprises of an injectable diagnostic drug ($^{13}$C-methacetin, 'LiMAxetin'); a LiMAx FLIP medical device and LiMAx breathing masks. To do a test, $^{13}$C-methacetin (which is labelled with a stable isotope and is not radioactive) is given by intravenous injection. The drug is metabolised by the liver-specific CYP1A2 enzyme into $^{13}CO_2$ and a small sub-therapeutic amount of paracetamol. Using continuous breath analysis, the LiMAx FLIP medical device measures the change in the ratio of $^{13}CO_2$ compared with $^{12}CO_2$. The change in ratio is combined with the patient's body weight to provide a measure of CYP1A2 activity, expressed as a LiMAx value as micrograms per kilogram per hour. The LiMAx value can be determined within 60 minutes and is used to stratify the patient's functional liver capacity into 3 levels of impairment: normal liver function (more than 315 micrograms per kilogram per hour), limited impairment (140 to 314 micrograms per kilogram per hour) and significant impairment (0 to 139 micrograms per kilogram per hour).

An algorithm has been developed for using the test in evaluating patients before liver surgery (Stockmann et al. 2010). It represents a clinical decision tree, based on preoperative LiMAx test results, to support surgical planning in people with a risk of pre-

existing liver injury or a planned resection of 2 or more segments. If preoperative LiMAx values indicate normal function, resections of up to 4 segments can be done. In patients with limited impairment or in whom major resection (more than 4 segments) is planned, clinical decisions should also be guided by preoperative liver or tumour volume analysis (for example by computed tomography volumetry). Depending on future remnant liver function (FRLF), resections are classed as either regular (FRLF more than 150 micrograms per kilogram per hour), feasible (FRLF 100 to150 micrograms per kilogram per hour) or critical (80 to 100 micrograms per kilogram per hour), or should not be considered (FRLF less than 80 micrograms per kilogram per hour). For this last group, alternative preoperative options could be considered to improve remnant liver volume (such as portal vein embolisation). Patients with significant impairment should not be considered for surgery and alternative management options should be considered.

LiMAx should not be used in people who are allergic to paracetamol because a small amount is produced during the test. People with an allergy to silicone should also not use LiMAx, because it is present in the LiMAx breathing mask.

# Innovations

The LiMAx system uses a novel marker of liver function capacity, which is measured at point-of-care. It is claimed that current tests are not reliable enough to predict or monitor post-operative complications and mortality after liver surgery or liver transplant.

# Current care pathway

The European Association for the Study of the Liver (EASL) clinical practice guidelines on hepatocellular carcinoma (HCC) recommend tailored treatment based on tumour stage, location and how well the patient's liver function is preserved. Although surgical approaches (liver resection or liver transplant) are the main treatments for people with liver cancer, non-surgical options can include thermal ablation, chemoembolisation, systemic chemotherapy and best supportive care (terminal stage).

Liver resection is recommended first-line treatment in people with liver cancer with a non-cirrhotic liver. In cirrhosis, only patients with well-preserved liver function are eligible for resection because of the high risk of post-operative decompensation. Suitability for surgery will depend on a multiparametric evaluation including the Child classification and Model for End-Stage Liver Disease (MELD) score, among other parameters, which

together aim to assess liver function reserve and estimate perioperative mortality. The type of surgical technique used for resection will depend on the size and location of the tumour. NICE has published interventional procedures guidance on laparoscopic and radiofrequency-assisted liver resection surgery, as well as ex-vivo hepatic resection and reimplantation. Transplant is recommended in people with liver cancer for whom resection is not suitable, but who stay within Milan criteria for liver transplant (a solitary tumour measuring 5 cm or less and up to 3 nodules measuring 3 cm or less).

According to policies set out by NHS England and the Liver Advisory Group (LAG) of NHS Blood and Transplant (NHSBT), the conditions considered for transplant in adults include acute liver failure, chronic liver failure, liver cancer, and variant syndromes. People needing a transplant are classed as 'super-urgent' (those who have sudden liver failure and are likely to die unless transplanted) or 'elective'. The criteria for an elective transplant, which are set out by the Liver Advisory Group, include people with chronic liver disease who are likely to die within 1 year unless they have a transplant and people with liver cancer for whom a resection is not suitable, as stated above. Prognostic models, such as MELD and United Kingdom Model for End-Stage Liver Disease (UKELD), can help predict survival on the waiting list. Both of these scores are used nationally to list patients (minimal listing criteria is a UKELD score of at least 49) and prioritise those on transplant waiting lists. Like MELD, UKELD is also derived from the patient's serum creatinine and bilirubin and International Normalised Ratio (INR) of the prothrombin time, but it also incorporates information about the patient's serum sodium level. The decision to recommend a transplant is agreed by a multidisciplinary team involving a transplant hepatologist and surgeon. Long-term transplant care should be given by consultant hepatologists in specialist wards and outpatient clinics.

# Population, setting and intended user

The LiMAx test would be used as well as current standard tests for the quantitative assessment of liver capacity in adults under evaluation for liver surgery or transplant. The test would be done by any healthcare professional who is authorised to administer intravenous drugs, and results would be interpreted by a medical specialist. The test can be done in an outpatient clinic, intensive care unit, recovery room or standard hospital ward setting. Adoption of the LiMAx system would not need substantial changes to the current care pathway, but operators will need a limited amount of product-specific training. Free on-site training is provided by the company when the device is purchased.

# Costs

## Technology costs

The LiMAx test consists of the LiMAx test kit (single use breathing mask and LiMAxetin diagnostic drug) and LiMAx FLIP reusable breath analysis device. The cost of each LiMAx test is £341 (excluding VAT) based on a minimum annual order of 50 test kits per year. The purchase cost is expressed as an annual charge of £17,050 and includes 1 LiMAx FLIP breath analysis device and 2 LiMAx test training sessions but excludes shipment costs. Since 2 tests are done per patient (before and after surgery), a LiMAx test has a per-patient cost of £682. All technology costs were converted from Euro at a rate of 0.88 pound sterling to 1 Euro.

## Costs of standard care

The company identified no currently available comparable real-time technology. Indocyanine green plasma disappearance rate (ICG-PDR) was identified by specialist commentators as an alternative method of evaluating overall liver function, but it is not widely used across the NHS.

# Resource consequences

The LiMAx test would be an additional cost to standard investigations of liver function such as biochemical tests or imaging techniques. These costs may be offset if the test allows less expensive management on the basis of predicting post-operative management, for example through a reduced length of stay in hospital.

If adopted, no substantial changes to the current care pathway or to facilities or infrastructure would be needed.

# Regulatory information

Components of the LiMAx system (LiMAx FLIP detection device and breathing masks only) are CE marked as class IIa medical devices. The technology also includes LiMAxetin solution for injection, a pharmaceutical diagnostic drug licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) for use as a 4 mg/ml solution for injection,

administered by an intravenous bolus injection at a standard dose of 2 mg/kg.

# 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).

The Equality Act 2010 considers a diagnosis of cancer as a disability. Therefore, individuals with liver cancer, or who have had liver cancer in the past, are automatically protected by the Act. Some people with chronic liver failure and people having or recovering from liver surgery or a liver transplant may be considered disabled under the Equality Act if their condition 'has a substantial and long-term adverse effect on their ability to carry out normal day-to-day activities'. LiMAxetin should not be used in children and adolescents under the age of 18 years. Age is a protected characteristic under the Equality Act 2010.

# Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. 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

The evidence base for the LiMAx system includes over 20 studies or case reports identified as being potentially relevant, covering clinical areas such as surgery, transplant, intensive care and hepatology.

Six studies (1 multicentre randomised controlled trial [RCT] trial and 5 observational studies), involving over 1,800 patients are included in this briefing. Studies were selected based on their relevance to this briefing as well as the quality of evidence. Table 1 summarises the clinical evidence as well as its strengths and limitations.

# Overall assessment of the evidence

The evidence suggests that LiMAx may provide a useful preoperative tool for risk stratification of patients being considered for liver surgery, including those with primary or secondary liver tumours with or without cirrhosis. Data show that the technology can accurately predict residual liver function capacity as well as post-operative liver failure and mortality. Data from 1 RCT, which involved 148 patients with intrahepatic tumours scheduled for liver surgery, showed that surgical decisions guided by pre- and post-operative LiMAx values were associated with substantial clinical impact. These include reductions in admissions to intensive care, lower rates of severe complications and a shorter length of intensive care and overall hospital stay. Data from observational studies have also shown that the use of LiMAx testing to guide surgical decisions was associated with an increase in the proportion of patients, including those with cirrhosis, having curative liver resection and a reduction in the rate of post-operative liver failure and liver failure-related mortality.

There is less evidence for a potential role for LiMAx in liver transplant, including the assessment of initial graft dysfunction immediately after transplant. Evidence also suggests the technology may be used as an aid for decision making around donor allocation by evaluating the short-term survival in liver transplant candidates. However, evidence for its predictive power for initial graft dysfunction came from a small number of patients (8 patients with true initial graft dysfunction) and the evidence for its use as a decision-making tool for organ allocation excluded patients with liver cancer and those with acute liver failure. As such, the results may not be transferable to the whole population of patients needing a liver transplant.

Overall, it is uncertain how generalisable the results are to UK NHS practice because all of the studies were done in Germany, with most evidence coming from a single centre. Further multicentre, RCTs that include NHS centres would be useful to confirm the available evidence has relevance to a UK population.

## Table 1 Summary of selected studies

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| Stockmann et al. (2018) | |
| Study size, design and location | Phase III, multicentre, 2-arm, parallel-group, open-label RCT involving 148 randomised adult patients (≥18 years) with intrahepatic tumours scheduled for open liver resection of at least 1 segment. Done in 6 German academic centres specialised in complex liver surgery. |
| Intervention and comparator(s) | Intervention: LiMAx (n=58).<br>Comparator: Standard of care (n=60). |
| Key outcomes | In the intervention group, the LiMAx test was done before and after surgery for individual surgical planning and to prospectively determine the level of post-operative care, respectively. 62% (n=36/58) of patients in the LiMAx group were transferred directly to a general ward after surgery versus 2% (n=1/60) of patients in the control group (p<0.001). The rate of severe complications (grade ≥IIIa) was significantly lower in the LiMAx group compared with the control group (14% versus 28%; p=0.022). No statistically significant differences were seen for grade I or II complications. Compared with the control group, patients in the LiMAx group had a significantly shorter length hospital stay after surgery (10.6 versus 13.3 days; p=0.012), as well as shorter length of immediate care/ICU (0.8 versus 3.0 days; p<0.001). |
| Strengths and limitations | Study compared the technology to standard of care and was sufficiently powered to detect between-group differences. Randomisation helped reduce the risk of selection bias. Surgical techniques used were not significantly different between treatment groups.<br>The study was funded by the company and carried out in Germany. Centres specialised in complex liver surgery, and people with complex liver resections and those with previous resections or pre-existing fibrosis or cirrhosis were excluded from this study; results may not fully reflect real-world clinical practice. All outcomes were hospital process measures. |
| Jara et al. (2015a) | |

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| Study size, design and location | Retrospective analysis involving 1,170 consecutive patients having elective liver surgery between January 2006 and December 2011, a period spanning the introduction of the LiMAx algorithm in 2008 and 2009. By 2010, LiMAx and its algorithm were fully integrated into clinical practice at the study centre. |
| Intervention and comparator(s) | Intervention: LiMAx test.<br>No comparator. |
| Key outcomes | The proportion of complex liver surgeries increased from 29.1% in 2006 to 37.7% in 2011 (p=0.034). The proportion of patients with cirrhosis who were selected for liver surgery increased from 6.9% in 2006 to 11.3% in 2011 (p=0.039). Rates of liver failure after liver surgery decreased from 24.7% in 2006 to 0.9% in 2011 (p=0.014). Similar results were seen in an analysis for a propensity-score matched cohort, where reductions in the rates of liver failure (24.7% [n=77] versus 11.2% [n=35]; p<0.001) and related mortality (3.8% [n=12] versus 1.0% [n=3]; p=0.035) after liver surgery were shown. |
| Strengths and limitations | Data were from a large number of consecutive and non-selected patients submitted for partial liver surgery, overcoming potential selection bias. Liver surgeries followed a common surgical approach and most (70.8%) were done by 3 experienced liver surgeons, reducing the risk of performance bias.<br>The study was a single-centre analysis done in Germany. The potential effect of improved surgical techniques, anaesthetic care and intensive care nursing over the study period cannot be excluded. Data on the number of patients who were denied surgery based on actual LiMAx values were not available so this study only provides low-level evidence on diagnostic accuracy. |
| Jara et al. (2015b) | |
| Study size, design and location | Single-centre prospective analysis of 167 patients with chronic liver failure without HCC evaluated for liver transplant between July 2009 and April 2013. |
| Intervention and comparator(s) | Intervention: LiMAx test.<br>MELD and ICG-PDR were evaluated as reference standards. |

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| Key outcomes | Within 6 months of follow-up, 36 had liver transplant and 18 patients died. Median LiMAx values were significantly lower in liver transplant candidates who died versus those who survived (99 versus 50 micrograms per kilogram per hour), while ICG-PDR did not differ between the 2 patient groups (4.4 versus 3.5%/min; p=0.159). When identifiable cut-off values for predicting the probability of death within 6 months were applied, LiMAx had a higher negative predictive value (0.93), compared with ICG-PDR (0.90) and MELD (0.91). |
| Strengths and limitations | Study involved consecutive enrolment of all patients fulfilling inclusion criteria. Study had a follow-up of 6 months and included other liver function parameters as reference.<br>Single-centre study conducted in Germany. MELD scores were relatively low for liver transplant candidates, perhaps because of the exclusion of patients with acute onset of liver failure. Patients with HCC were excluded from the study. It is unclear whether all patients in this study were eligible for transplant and how the availability of suitable donors affected this. |
| Stockmann et al. (2010) | |
| Study size, design and location | Observational trial involving 329 patients with liver tumours evaluated for liver surgery. |
| Intervention and comparator(s) | Intervention: LiMAx test. |

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| Key outcomes | Blinded preoperative mean LiMAx values (study group) were significantly higher before resection (351 micrograms per kilogram per hour, n=139) versus before refusal (299 micrograms per kilogram per hour, n=29; p=0.009). In-hospital mortality rates were 38.1% (8/21 patients), 10.5% (2/19 patients) and 1.0% (1/99 patients) for post-operative LiMAx of <80 micrograms per kilogram per hour, 80 to 100 micrograms per kilogram per hour and >100 micrograms per kilogram per hour, respectively (p<0.0001). LiMAx levels <80 micrograms per kilogram per hour were associated with longer hospital stays and duration of intensive care. After developing a decision tree, its prospective preoperative application (routine group) also revealed higher LiMAx values before resection versus before refusal (257 versus 356 micrograms per kilogram per hour; p<0.0001). Intra-hospital mortality after surgery reduced from 9.4% in the blinded study group to 3.4% in the routine group (p=0.019). |
| Strengths and limitations | Selection of patients was not influenced by individual characteristics and medical personnel were blinded to preoperative LiMAx readouts.<br>Single-centre study done in Germany. Outcome and survival in the study group were only followed up until discharge from the hospital. There were significant between-group differences in aetiology and surgical procedures. Potential parameters that might bias the individual test result including obesity, tumour stage and the general condition of the patient cannot be excluded. |
| Lock et al. (2010) | |
| Study size, design and location | Prospective, observational, pilot study involving 99 patients having deceased donor liver transplant between August 2005 and May 2007. |
| Intervention and comparator(s) | Interventions: the LiMAx test.<br>Comparators: ICG-PDR, and conventional biochemical parameters for the diagnosis of initial graft dysfunction. |

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| Key outcomes | Patients with initial graft dysfunction had lower LiMAx values immediately after transplant (43 versus 184 micrograms per kilogram per hour; p<0.001) whereas ICG-PDR was only slightly decreased (11.8 versus 15.5 %/min; p=0.200). Significant differences were also seen for serum bilirubin, ammonia, glutamate dehydrogenase, and the INR (p<0.05). Multivariate analysis showed LiMAx to be the only single independent predictor of initial graft dysfunction (p<0.008). ROC analysis for LiMAx showed an AUROC curve of 0.960 (p<0.001). LiMAx was shown to detect initial graft dysfunction with a sensitivity of 1.0, specificity of 0.92, a positive predictive value of 0.53, and a negative predictive value of 1.0. The LiMAx and AST were used to detect primary non-function (PNF; n=3) on the first post-operative day. AUROC values were 0.992 (p=0.004) for LiMAx and 0.967 (p=0.006) for AST. Based on a combination of test results obtained immediately after transplant and on the first day, LiMAx was shown to detect diagnose PNF with a sensitivity of 1.0 and a positive predictive value of 1.0, while AST showed a sensitivity of 0.67 and a positive predictive value of 0.29. LiMAx showed significantly better diagnostic accuracy versus AST (p=0.031) for the diagnosis of PNF within 24 hours after transplant. |
| Strengths and limitations | Study compared LiMAx to ICG-PDR test and conventional biochemical parameters and post-operative outcomes were documented for 90 days. LiMAx and ICG-PDR were done by doctors who were not involved in clinical management and surgical re-intervention was decided independent of study results.<br>Data comes from 1 German centre. Immediate graft dysfunction was retrospectively defined from the patient's history. LiMAx cut-off values were determined post hoc from the same data set. Extrahepatic factors affecting LiMAx values such as co-administration of catecholamines and weight changes after transplant cannot be excluded. |
| Stockmann et al. (2009) | |
| Study size, design and location | Single-centre, prospective observational study involving 64 adult patients (18 to 75 years) having liver surgery between August 2004 and February 2007. |

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| Intervention and comparator(s) | Intervention: LiMAx test. |
| Key outcomes | Residual LiMAx values on post-operative day 1 showed significant correlation with residual liver volume (r=0.94; p<0.001). Multivariate analysis showed LiMAx to be the only predictor of liver failure (p=0.003) and mortality (p=0.004) on post-operative day 1. ROC analysis showed an AUROC of 0.99 for the prediction of both liver failure and liver failure-related death by LiMAx and an AUROC of 0.69 for severe complications. LiMAx was shown to predict liver failure related death with a sensitivity of 1.0 and a specificity of 0.93. An accurate calculation of the remnant liver function capacity before surgery was measured by combining computed tomography volumetry and LiMAx (r=0.85; p<0.001). No adverse events of the intravenous $^{13}$C-methacetin administration were observed during injection or follow-up. |
| Strengths and limitations | Patients were followed up for a total of 6 months and none of the patients withdrew consent. LiMAx measurements were validated in healthy volunteers and also during anhepatic phase of liver transplant. Histopathology evaluation was done by a blinded pathologist.<br>Data come from a single German centre. |
| Abbreviations: AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic; ICG-PDR, indocyanine green plasma disappearance rate; ICU, intensive care unit; INR, internal normalised ratio; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; RCT, randomised controlled trial; ROC, receiver operating characteristic. | |

# Recent and ongoing studies

- The CLiFF Study: Change in Liver Function and Fat in Pre-operative Chemotherapy for Colorectal Liver Metastases. ClinicalTrials.gov identifier: NCT03562234. Status: Recruiting. Indication: Colorectal Cancer, Liver Metastasis Colon Cancer, Chemotherapy Effect. Intervention(s): LiMAx, MR.

- The company state that LiMAx is currently being used in 8 clinical studies in indications such as malignant liver disease, major liver resection, liver resection, bariatric surgery, non-alcoholic fatty liver disease (NALFD), non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma.

# Specialist commentator comments

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

Six out of 8 of the specialist commentators said they were familiar with the technology, 1 of whom had used the device in a research setting.

## Level of innovation

Most of the commentators agreed that the technology was a novel concept, although 1 commentator believed it was a variation of an existing modality (ICG-LiMON) for assessing liver function. One commentator noted that, although other quantitative measures of liver function are available, it is innovative in that it uses a single-breath test after injecting a diagnostic drug. Another commentator said that the technology is likely to be of prognostic value, but more data are needed before widespread implementation. Good tests for liver function capacity was highlighted by 1 of the commentators as an area of unmet need. Another specialist said that existing strategies lack accuracy and the selection of patients for surgery is based on a crude assessment of liver function. Two of the commentators were not aware of any competing technologies, while all other commentators identified plasma disappearance rate of indocyanine green (ICG-PDR) as an alternative to LiMAx. Hepatobiliary scintigraphy was also identified by 1 commentator, who noted that the scan can provide an estimation of future remnant liver function; which they stated was the most useful information for surgeons. One commentator thought that the technology provided similar information to ICG-PDR and that there is more experience of ICG-PDR in the UK.

## Potential patient impact

Improved risk stratification, better patient selection for liver resection and transplant, and improved assessment of graft function after liver transplant were mentioned by

commentators as potential benefits to patients. One commentator said that the technology could help avoid surgery in high-risk patients, while another said the technology could help identify patients who would be suitable for preoperative procedures aimed at improving liver remnant before surgery. The non-invasive nature of the test was also highlighted as a patient benefit by 1 commentator. Most of the specialists believe the technology has the potential to either change the current care pathway or improve clinical outcomes in the UK, although 4 noted that more data would be needed to support this. One commentator noted that the technology would always be part of a multiparametric assessment, so direct correlation between the test and clinical outcomes (morbidity, mortality and length of stay) may be difficult to determine. One commentator said that studies from a German centre have already shown a change in the care pathway after adoption of the technology. When commenting on the groups of people who would benefit most from the technology, 5 of the experts identified people with cirrhosis who are having liver resection. People being considered for major resection and those at high risk of complications were also mentioned. Another commentator thought that the test had the most benefit in identifying suitable transplant donor organs. One commentator thought that the group of patients who would benefit was not yet clearly defined.

# Potential system impact

The commentators said the technology may assist surgical planning through improved risk stratification of people with liver disease. According to some of the specialists, there is the potential to reduce intensive care unit resource and hospital mortality by reducing post-operative liver failure, and may contribute to better intensive care unit use after surgery. One commentator said that the technology has the potential to help standardise national protocols for liver resection. Another commentator thought it may provide system benefits, mainly through helping to identifying donor organs with good liver function. One commentator did not think the test would have a wide effect on the healthcare system because mortality rates after surgery are low and most surgeries can be done safely. Most commentators thought LiMAx would be used as an add-on test to standard of care, with 1 commentator saying that it may replace ICG-PDR in some centres. One commentator said LiMAx would cost more than standard of care and another said it would be cost incurring in the short term. Three commentators said the technology has the potential to provide cost-savings but only if it leads to shorter hospital/intensive care stays for patients or reduces the risk of post-operative complications. Two commentators said the cost implications were unclear because of the lack of economic analyses, with 1 specialist adding that the technology should be cost neutral but further data are needed. One commentator thought that the technology could lead to an increase in surgery on high-risk

patients and another specialist said that the test may lead to more portal vein embolisation procedures. Additional staff time and the need for staff resource to do the test, product-specific training need as well as logistical issues, such as the purchase, storage, transport and maintenance of equipment, were other factors thought to effect resource. One commentator said that the effect on resources was not yet clear but is expected to be very modest. Most of the specialists expect minimal or no changes to facilities or infrastructure to use the technology. Purchase of the LiMAx equipment and staff training were said to be the only other needs.

## General comments

None of the commentators were aware of any safety concerns or regulatory issues. One commentator said that there is a potential risk of allergic reaction to methacetin but was not aware of any reports of this to date. All of the commentators said that the technology is not yet widely used in the UK but most were not aware of any major barriers to adoption. Three commentators thought the main issues for adoption surrounded the available evidence base, particularly the lack of evidence in an NHS setting. The cost of the technology was mentioned as another potential issue for adoption. Most commentators thought that UK NHS-based studies were needed, which could be via post-marketing studies after implementing the test. One commentator noted that LiMAx threshold values for risk stratification should to be validated in other centres before it can be used in clinical practice. One commentator said the technology could be used as a point-of-care test, both in the in-patient and outpatient setting but only in secondary or tertiary care. Two commentators thought the role of the technology in liver transplant was unclear from available evidence. One of the commentators added that it should be used with caution when assessing liver function after transplant but could potentially be used to assess organ-donor graft function. One commentator said that the test seems technically involved while all other commentators said there were no issues with the usability or the practical aspects of the technology. One commentator said the test is easy to use but is not convinced it has substantial advantages over ICG-PDR at present. Another specialist said that, based on regular use in Germany, the test appears to provide unique insight into the functional capacity of the liver.

# Specialist commentators

The following clinicians contributed to this briefing:

- Professor Andrew Renehan, professor of cancer studies and surgery, University of Manchester and the Christie NHS Foundation Trust, Humedics have provided financial support to the University of Manchester for the CLiFF project.
- Dr Michael Heneghan, clinical director for liver services, Consultant Hepatologist & Professor of Hepatology, Institute of Liver Studies, King's College Hospital, did not declare any interests.
- Professor Rajiv Jalan, professor of hepatology, editor in chief: Journal of Hepatology Head, Liver Failure Group, ILDH, Division of Medicine, UCL Medical School, has indirect interest from 2015 to present: has research collaborations with Takeda and Yaqrit, and is a consultant for and founder of Yaqrit Limited. He is the inventor of the following hepatological treatments: ornithine phenylacetate, Yaq-001, DIALIVE and Yaq-005.
- Dr Tahir Shah, consultant hepatologist and transplant physician, Head of Birmingham Neuroendocrine Tumour Centre, University Hospitals Birmingham NHS Foundation Trust, did not declare any interests.
- Mr Robert Sutcliffe, consultant in hepatobiliary and pancreatic surgery, University Hospitals Birmingham NHS Foundation Trust, did not declare any interests.
- Dr Abid R Suddle, consultant hepatologist and liver transplant physician, Institute of Liver Studies, King's College Hospital, did not declare any interests.
- Mr Keith Roberts, consultant liver transplant, hepatobiliary and pancreatic surgeon, honorary reader, University of Birmingham, did not declare any interests.
- Mr Bobby V M Dasari, consultant hepatopancreatobiliary surgeon, University Hospitals Birmingham NHS Foundation Trust, currently evaluating the role of Hepatobiliary Scintigraphy with SPECT-CT, ICG-PDR, fibroscan, wedge pressures to predict and prevent post-hepatectomy liver failure.

# Development of this briefing

This briefing was developed by NICE. 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.

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