National Institute for Health and Care Excellence

Diagnostics consultation document

Tests for rapidly identifying bloodstream bacteria and fungi (LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay)

The National Institute for Health and Care Excellence (NICE) is producing guidance on using the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay in the NHS in England. The Diagnostics Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report) which is available from http://www.nice.org.uk/guidance/indevelopment/gid-dt25.

The Advisory Committee is interested in receiving comments on the following:

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

Equality issues

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

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology

- could have any adverse impact on people with a particular disability or disabilities.

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

Note that this document is not NICE's final guidance on the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay The recommendations in section 1 may change after consultation.

After consultation, the Committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the Committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the Diagnostics Assessment programme manual (available at https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-diagnostics-guidance).

Key dates:

Closing date for comments: 21 October 2015

Second Diagnostics Advisory Committee meeting: 4 November 2015

1 Provisional recommendation

1.1 There is currently insufficient evidence to recommend the routine adoption in the NHS of the SeptiFast LightCycler Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi. The tests show promise and further research to provide robust evidence is encouraged, particularly to demonstrate the value of using the test results in clinical decision-making (see sections 5.18 to 5.22).

2 Clinical need and practice

The problem addressed

2.1 In current practice, people who are clinically unwell and who have a suspected bloodstream infection are given empirically prescribed

broad-spectrum antibiotics until the identity of the pathogen causing the infection is known. Broad-spectrum antibiotics and, where appropriate, antifungals, are given because they are effective against a wide range of bacterial and fungal pathogens and are likely to achieve a therapeutic response. However, despite being clinically effective, the use of broad-spectrum antibiotics is associated with people developing superinfection and the development of antimicrobial resistance. Reducing the length of use of broad-spectrum antibiotics may contribute to antimicrobial stewardship and help to conserve the effectiveness of existing antimicrobials. Rapidly identifying the bacterial and fungal pathogen may enable earlier targeted treatment and reduce the length of use of broad-spectrum antibiotics.

2.2 Three molecular tests, the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay, were identified during scoping as relevant to the assessment (see section 3 for additional details). These tests are designed to rapidly detect and identify bacterial and fungal DNA that may be present in the bloodstream in people who are suspected of having sepsis. These tests are intended to be used with clinical assessment and established microbiology techniques that provide information on which antimicrobials are likely to be effective against the identified pathogen. The tests are designed to be run on whole blood samples and without the prior incubation or the pre-culture steps that are needed for tests used in current standard practice. The absence of these steps means that pathogens may be identified earlier. It is anticipated that blood culture would still be needed to provide definitive antimicrobial-susceptibility data, if this is not provided by the rapid diagnostic test. The rapid detection and identification of bacterial and fungal DNA may be of particular benefit in people who are suspected of having a severe infection and who need prompt medical intervention.

2.3 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi in the NHS.

The condition

Sepsis and bloodstream infection

2.4 Sepsis is a life-threatening condition characterised by the body's inflammatory response to an infection. According to the Surviving Sepsis Campaign's International guidelines for the management of severe sepsis and septic shock, sepsis is diagnosed if there is evidence of systemic inflammation, in addition to a documented or presumed infection in the body. Systemic illness often occurs if bacteria invade normally sterile parts the body. One example of this is when bacteria or fungi invade the bloodstream (bloodstream infection), a process that often causes an inflammatory immune response.

2.5 Bacterial infections are the most common cause of sepsis and bloodstream infection, but they can also be caused by fungal infections, and less commonly by viral infections. The most common sites of infection associated with sepsis are the lungs, urinary tract, abdomen and pelvis. Other sources of infection leading to sepsis include skin infections (such as cellulitis), post-surgical infections and infections of the nervous system (such as meningitis or encephalitis).

2.6 People who have recently been hospitalised are at risk of getting hospital-acquired infections that can lead to sepsis and bloodstream infection. It is thought that the increased use of invasive procedures, such as catheterisation and life support measures, as well as immunosuppressive therapy and antibiotic therapy have resulted in more healthcare-associated bloodstream

infections. Community-acquired bloodstream infections may also occur in people who have not had recent contact with healthcare services. The pathogens isolated from these people may differ from those associated with hospital-acquired bloodstream infection.

2.7 The bacteria most commonly associated with bloodstream infection in adults include gram-negative species such as *Escherichia coli*, *Klebsiella* and *Pseudomonas*, and gram-positive species such as *Staphylococcus aureus*, *non-pyogenic streptococci*, *Enterococcus* and *Streptococcus pneumoniae*. The types of pathogens causing bloodstream infection can differ in children compared with those isolated from adults, and can include *Neisseria meningitidis*. In addition, polymicrobial infection and anaerobic bacteraemia are thought to occur less often in children.

The diagnostic and care pathways

Diagnosing sepsis and bloodstream infection

2.8 Diagnostic criteria for sepsis are listed in the Surviving Sepsis Campaign's International guidelines for the management of severe sepsis and septic shock. In summary, regular observations of all vital signs should be taken and recorded, kidney and liver function tests should be done, and inflammatory biomarkers and serum lactate should be measured. These guidelines state that a diagnosis of sepsis should be based on infection, documented or suspected, with hyperthermia or hypothermia, tachycardia and at least one indication of altered organ function.

2.9 The guidelines also make the following specific recommendations relating to the detection of localised and bloodstream infection:

- At least 2 samples for blood culture should be collected (aerobic and anaerobic) before antimicrobial therapy is started if such cultures do not cause significant delay (greater than 45 minutes)

in the start of antimicrobial administration. At least 1 sample should be drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (less than 48 hours) inserted. The blood cultures can be drawn at the same time if they are taken from different sites. Cultures from other sites that may be the source of infection, such as urine, cerebrospinal fluid, wounds, respiratory secretions or other bodily fluids, should be collected before starting antimicrobial therapy, if doing so does not cause significant delay in the start of antimicrobial treatment.

- Imaging studies such as CT or X-ray should be done to confirm a potential source of infection.
- Assays to diagnose systemic fungal infection should be used if available and invasive candidiasis is suspected.

Blood cultures

2.10 Standards for the investigation of blood cultures are available from Public Health England. A blood culture set for the diagnosis of bloodstream infection is defined as 1 aerobic and 1 anaerobic bottle. For adults it is recommended that 20–30 ml of blood is cultured per set, and that 2 consecutive blood culture sets from 2 separate venepuncture sites should be collected during any 24-hour period for each septic episode. The first set should be taken before starting antimicrobial treatment because the presence of antibiotics or antifungals may inhibit the growth of pathogens in blood culture. Blood culture sample collection differs for infants and neonates, for whom a single aerobic bottle or low-volume blood culture bottle may be requested. The criterion for calculating total blood-culture volume in neonates and children is based on weight rather than age and relates to total patient blood volume. It has been suggested that the volume of blood drawn should be no more than 1% of the patient's total blood volume. In infants and children the magnitude of bacteraemia is usually higher than that in adults

and therefore the sensitivity of detection is not thought to be significantly reduced by a lower blood-to-medium ratio.

2.11 Blood culture bottles should be incubated within 4 hours of the blood sample being taken. Many laboratories now use automated culture systems that alert laboratory staff once growth has been detected.

2.12 When a blood culture has been detected as positive it is recommended that:

- Gram staining and rapid antigen testing should be done within 2 hours.
- Direct or automated isolate identification should be done within 24 hours (extending to 48 hours if traditional microbiology techniques such as morphological identification are used). Rapid species identification may be done after blood culture using techniques such as MALDI-TOF mass spectrometry.
- Identification should be followed by sensitivity testing to determine to which antimicrobials the identified pathogen is susceptible. If direct or automated sensitivity testing is used, a report should be made within 24 hours, extended to 48 hours if traditional techniques such as the disc diffusion method are used.
- A preliminary positive report is made within 2 hours of identification and sensitivity testing, and a final positive report should be made within 5 days of the sample arriving in the laboratory.

2.13 If a blood culture is negative, it is recommended that a preliminary negative report is provided within 48 hours of sample receipt in the laboratory and a final negative report should be issued within 5 days unless extended culture is being done, such as if fungi or unusual, fastidious or slow growing organisms are suspected.

Treating sepsis and bloodstream infection

2.14 The treatment of sepsis varies based on the initial infection, the organs affected and the extent of tissue damage. The management of severe sepsis and septic shock is described in the Surviving Sepsis Campaign's International guidelines for the management of severe sepsis and septic shock.

2.15 The guidelines recommend that effective intravenous antimicrobials should be given within the first hour of recognition of severe sepsis and septic shock. Initial empiric antimicrobial therapy should include 1 or more drugs that have activity against all likely pathogens (bacterial, fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis. Frequently used broad-spectrum antibiotics for more serious infections include cephalosporins and aminoglycosides.

2.16 The guidelines recommend that the choice of empirical antimicrobial therapy be based on:

- the patient's history, including drug intolerances
- recent antibiotics treatments (previous 3 months)
- underlying disease
- the clinical syndrome
- susceptibility patterns of pathogens in the community and hospital
- previous microbiology reports identifying pathogens that have previously colonised or infected the patient.

2.17 It is recommended that clinicians prescribing antimicrobial therapy should take into account the Department of Health's guidance on antimicrobial stewardship, which is based on the 'start smart then focus' strategy. The guidance recommends that, when empirical antimicrobials are prescribed, the clinical diagnosis should be reviewed after 48 to 72 hours to allow an antimicrobial prescribing

decision to be made. This decision should take into account available microbiology results to determine if therapy can be stopped or changed; that is, the de-escalation, substitution or addition of antimicrobial agents to the treatment plan.

2.18 Narrowing the spectrum of antimicrobial coverage and reducing the duration of therapy is thought to be associated with a reduction in the risk of a person developing a superinfection, a reduction in treatment-related adverse events and a reduction in the selection of resistant organisms. Adverse events associated with the use of broad-spectrum antimicrobials may include diarrhoea, nausea, vomiting, hearing loss, damage to the kidneys and an increased risk of developing superinfection with *Clostridium difficile*. Narrowing the spectrum of antimicrobial coverage may also be associated with an increase in treatment efficacy in some scenarios.

2.19 Surveillance data for England for the period 2010 to 2013 suggest that rates of methicillin-resistant *Staphylococcus aureus* (MRSA) have fallen while the incidence of bloodstream infections caused by resistant gram-negative Enterobacteriaceae bacteria, such as *Klebsiella* and *Escherichia coli*, has increased (English surveillance programme for antimicrobial utilisation and resistance, 2014). Of particular concern in some regions of England is the increasing resistance to carbapenem antibiotics, which are often used as a last resort for treating severe infections.

3 The diagnostic tests

The interventions

The LightCycler SeptiFast Test MGRADE

3.1 The LightCycler SeptiFast Test MGRADE (Roche Diagnostics) is a CE-marked, in-vitro, diagnostic, real-time polymerase chain

reaction (PCR) test that simultaneously detects and identifies DNA from 25 bacterial and fungal pathogens. The test needs 1.5 ml of ethylenediaminetetraacetic acid (EDTA)-treated whole blood.

3.2 The LightCycler SeptiFast Test MGRADE involves 3 distinct processes: specimen preparation by mechanical lysis and purification of DNA, real-time PCR amplification of target DNA in 3 parallel reactions (gram-positive bacteria, gram-negative bacteria and fungi), and detection using fluorescence-labelled probes specific to the target DNA. The test takes a minimum of 6 hours, depending on laboratory workflow.

3.3 The SeptiFast Identification Software set v2.0 analyses the samples and generates a report, which contains all the relevant laboratory data and details of the identified species. The software also includes a crossing point cut-off rule, which is intended to reduce the positive rate for coagulase-negative *Staphylococci* and *Streptococcus* species based on the assumption that they are contaminants and not causal agents when the crossing point value is less than 20.

3.4 If *Staphylococcus aureus* is identified in a sample, an aliquot of the SeptiFast Test MGRADE eluate can be further tested for the presence of the MecA gene using the LightCycler SeptiFast MecA Test MGRADE. The test can determine the likely methicillin resistance of *Staphylococcus aureus* through PCR, using the LightCycler 2.0 instrument.

3.5 The test has an analytical sensitivity of 100 colony-forming units/ml for coagulase-negative *Staphylococci*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus pneumonia* and *Streptococcus mitis*. The minimum analytical sensitivity for all other pathogens detected by the LightCycler SeptiFast test MGRADE is 30-colony-forming units/ml.

SepsiTest

3.6 SepsiTest (Molzym Molecular Diagnostics) is a CE-marked PCR in-vitro test for detecting bacterial and fungal DNA in 1 ml of k-EDTA- or citrate-treated whole blood. The test is able to identify species from more than 200 genera of bacteria and 65 genera of fungi.

3.7 The SepsiTest involves 3 distinct processes: extracting and purifying microbial DNA using centrifugation, universal PCR and sequencing. The PCR result, which is available after 4 hours, indicates whether bacteria or fungi are present in the sample. Amplicons from positive samples are then sequenced to confirm the PCR result and to determine which bacteria or fungi species are present. Where readable sequences are available from sequence analysis, bacteria and fungi can be identified using the SepsiTest-BLAST online tool. Sequencing results may be available in 3–4 hours depending on the analyser used.

3.8 The analytical sensitivity of SepsiTest ranges from 10 to 80 colony-forming units/ml, depending on the target species.

IRIDICA BAC BSI assay

3.9 The IRIDICA BAC BSI assay (Abbott Diagnostics) is a CE-marked, in-vitro, diagnostic test for detecting and identifying DNA from bacteria and candida DNA in 5 ml of whole blood treated with EDTA. The test can also detect the mecA (*Staphylococcus*-specific methicillin resistance), vanA and vanB (*Enterococcus*-specific vancomycin resistance), and KPC (gram-negative associated carbapenem resistance) genes, which are associated with antibiotic resistance.

3.10 The test is designed for use with the IRIDICA system, which combines broad-range PCR with electrospray ionisation time-of-flight mass spectrometry to amplify and detect pathogens. The estimated time to result is at least 5 hours and 55 minutes.

3.11 The IRIDICA analysis computer consists of a proprietary database and software, which identifies the organism present in the sample by comparing the sequence of the sample with a library of known sequences.

3.12 The BAC BSI assay is able to identify more than 780 bacteria and candida. The mean limit of detection for the assay is 39 colony-forming units/ml, with a range of 0.25 to 128 colony-forming units/ml depending on the target species.

The comparators

3.13 Two comparators are included, blood culture alone and blood culture with MALDI-TOF mass spectrometry:

- Blood culture alone refers to the incubation of whole blood followed by the identification of pathogens by traditional microbiology techniques.
- Blood culture with MALDI-TOF mass spectrometry refers to the incubation of whole blood followed by the identification of pathogens using MALDI-TOF mass spectrometry.

4 Outcomes

The Diagnostics Advisory Committee (section 8) considered evidence from a number of sources (section 9).

How outcomes were assessed

4.1 The assessment consisted of a systematic review of the evidence on test performance and clinical-effectiveness data for the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI and comparator tests.

4.2 Studies were included if they evaluated 1 of the interventions, compared with either blood culture or blood culture with

MALDI-TOF mass spectrometry (MS), to analyse whole blood samples collected from people being treated for suspected sepsis. Studies that compared 1 of the interventions with another intervention were also included. In total, 66 studies met the inclusion criteria. Diagnostic-accuracy data were reported in 62 of the 66 studies and were included in meta-analyses, which were based on a bivariate normal model with Markov Chain Monte Carlo simulation. Inter-study heterogeneity was explored using meta-regression. Intermediate or clinical outcome measures were reported in 41 of the 66 studies and were included in a narrative analysis.

4.3 Sixty four of the 66 studies were single-index test, single-gate studies, that is, studies in which only patients with the target condition (suspected sepsis) were recruited. Three of these studies were randomised controlled trials (RCTs). The remaining 2 studies were single-gate studies that reported results for both the LightCycler SeptiFast Test MGRADE and SepsiTest.

4.4 Only 3 of the 66 studies included patients from the UK. Most of the studies were done in other European countries. Of the studies that included patients from the UK, 1 study (Dark et al. 2009) used the SeptiFast assay to test 50 patients and 1 other study (Vincent et al. 2015) used the IRIDICA assay to test 529 patients from 6 European countries. The third UK study (Warhurst et al. 2015) reported the use of SeptiFast in 795 patients with sepsis and was judged to be the highest quality and most applicable included study.

4.5 All studies were assessed using the QUADAS-2 tool. The results of 65 of the 66 studies were considered to be at risk of bias and may not be applicable to the decision problem. The issues of greatest uncertainty included patient selection and blinding to the index test

or reference standard. The External Assessment Group also reported concerns about 21 of the 66 studies, which did not report whether the blood samples for the index test and reference standard were drawn at the same time, and 6 of the 66 studies, which used a mixture of reference standards. In addition, only 28 of the 66 studies reported using blood sampling and test methods that were in accordance with the company's instructions for use. Studies also reported different units of analysis for diagnostic-accuracy data, such as per patient, per sample, per episode of sepsis, and species or pathogen level.

Diagnostic accuracy

4.6 Of the 62 studies that reported diagnostic-accuracy data, 55 reported data for the LightCycler SeptiFast Test MGRADE; 5 reported data for SepsiTest; and 4 reported data for the IRIDICA BAC BSI assay. Two of the 62 studies that reported data for both the Light Cycler SeptiFast Test MGRADE and SepsiTest were counted as individual studies for each test.

LightCycler SeptiFast Test MGRADE

4.7 There were 54 studies that compared the LightCycler SeptiFast Test MGRADE with blood culture and were combined in a meta-analysis. The pooled estimate for sensitivity was 0.65 (95% credible interval [CrI] 0.60 to 0.71; 95% prediction interval 0.29 to 0.90) and for specificity was 0.86 (95% CrI 0.84 to 0.89; 95% prediction interval 0.62 to 0.96). The proportion of discordant results varied across studies from 6% to 46% (median 17%).

4.8 One study (Tafelski et al. 2015) compared the LightCycler SeptiFast Test MGRADE with blood culture plus MALDI-TOF MS. It reported a sensitivity of 0.58 (95% confidence interval [CI] 0.30 to 0.86) and a specificity of 0.74 (95% CI 0.64 to 0.85).

4.9 Reasons for heterogeneity in sensitivity and specificity estimates between studies were explored using meta-regression for clinically relevant variables. The following variables were explored:

- age (neonates and children)
- exposure to antibiotics before blood sample collection
- suspected community- or healthcare-acquired infection
- febrile neutropenia
- studies with inclusion or exclusion of contaminants.

There was no evidence that sensitivity and specificity estimates were affected by these variables.

SepsiTest

4.10 Four studies compared SepsiTest with blood culture and were combined in a meta-analysis. The pooled estimate for sensitivity was 0.48 (95% CrI 0.21 to 0.74; 95% prediction interval 0.07 to 0.90) and for specificity was 0.86 (95% CrI 0.78 to 0.92; 95% prediction interval 0.66 to 0.95). The proportion of discordant results varied between studies and ranged from 14% to 26% (median 22%).

4.11 One study (Loonen et al. 2014) compared SepsiTest with blood culture plus MALDI-TOF MS. The study reported a sensitivity of 0.11 (95% CI 0.00 to 0.23) and specificity of 0.96 (95% CI 0.92 to 1.00). No subgroup analyses were possible for the SepsiTest.

IRIDICA BAC BSI

4.12 Four studies compared the IRIDICA BAC BSI assay with blood culture and were combined in a meta-analysis. Two of these studies reported data using an earlier version of the IRIDICA PCR/ESI-MS analyser known as the PLEX-ID system, which has different desalter and mass spectrometry modules. The pooled estimate for sensitivity was 0.81 (95% CrI 0.69 to 0.90; 95%

prediction interval 0.55 to 0.94) and for specificity was 0.84 (95% CrI 0.71 to 0.92; 95% prediction interval 0.50 to 0.96). The proportion of discordant results varied between studies and ranged from 7% to 30% (median 18%).

4.13 No studies compared the IRIDICA BAC BSI assay with blood culture plus MALDI-TOF MS and no subgroup analyses were possible for this intervention.

Intermediate and clinical outcomes

4.14 There were 41 studies included that reported data relating to the time to pathogen identification for the index test, time to treatment, test failure rate, mortality, duration of intensive care unit or hospital stay, duration of antibiotic therapy or reported changes in antimicrobial treatment plan. None of the included studies reported data on re-admission rates, adverse events associated with broad-spectrum antimicrobial use, morbidity, changes in disease severity over time, rates of superinfection, rates of resistant infection or health-related quality of life.

Light Cycler SeptiFast Test MGRADE

4.15 There were 37 studies that reported data on intermediate and clinical outcomes for the LightCycler SeptiFast Test MGRADE. In addition, 1 study (Schreiber et al. 2013) reported data for both the LightCycler SeptiFast Test MGRADE and SepsiTest. No studies compared the LightCycler SeptiFast Test MGRADE with the IRIDICA BAC BSI assay.

Time to result (pathogen identification)

4.16 There were 21 studies using the LightCycler SeptiFast Test MGRADE that reported turnaround times of a minimum of 4 hours to a median of 26.25 hours for pathogen identification. Some of these studies also reported the time for pathogen identification

using blood cultures, which ranged from a turnaround time of a minimum of 24 hours to a median of 80 hours.

Time to treatment change

4.17 Time-to-treatment change for the LightCycler SeptiFast Test MGRADE was reported in 3 RCTs:

- Tafelski et al. (2015) reported a mean time of 18.8 hours (standard deviation [SD] 5.6) from taking the blood sample to changing treatment using the LightCycler SeptiFast Test MGRADE and a mean time of 38.3 hours (SD 14.5) using blood culture and MALDI-TOF MS.
- Rodrigues et al. (2013) reported a mean time of 9.7 hours from taking the blood sample to a change in treatment using the LightCycler SeptiFast Test MGRADE compared with a mean time of 50.1 hours using blood culture (p=0.004).
- Idelevich et al. (2015) reported a mean time to changing treatment of 21.4 hours (range 16.2 to 46.3 hours) in the LightCycler SeptiFast Test MGRADE group compared with 47.5 hours (range 7.3 to 59.2 hours) in the blood culture group (p=0.018).

Test-failure rates

4.18 There were 7 studies that reported test failure rates for the LightCycler SeptiFast Test MGRADE, which ranged from 1.5% to 24.2%. It is not clear why there is a large variation in failure rates between studies.

Duration of stay in intensive care unit, hospital or both

4.19 Duration of stay in an intensive care unit, or hospital, or both were reported in 13 studies that compared the LightCycler SeptiFast Test MGRADE with blood culture. In most of these studies it was unclear if the duration of stay was recorded from before, during or after blood sampling. Also, most of the studies did not present

comparative data. Of the 4 studies that did report between group differences, 1 study (Alvarez et al. 2012) reported a statistically significant difference ($p<0.05$) in intensive care unit and hospital duration of stay in favour of the LightCycler SeptiFast Test MGRADE. Three other studies (Idelevich et al. 2014; Mancini et al. 2014; Rodrigues et al. 2013) reported no significant difference in duration of stay.

Duration of broad- and narrow-spectrum antibiotic therapy

4.20 One RCT (Tafelski et al. 2015) reported a duration of empirical antimicrobial therapy of 18.8 hours (SD ±5.6) for patients in the LightCycler SeptiFast Test MGRADE group compared with 38.3 hours (SD ±14.5) for patients in the blood culture with MALDI-TOF MS group.

Change in antimicrobial treatment

4.21 There were 14 studies that reported details of change in antimicrobial treatment, 10 of which did not report comparative data. Three compared the LightCycler SeptiFast Test MGRADE with blood culture. One RCT (Rodrigues et al. 2013) reported that therapy was adjusted for 35% of patients in the LightCycler SeptiFast Test MGRADE group compared with 24% of patients in the blood culture group. In contrast, a further RCT (Idelevich et al. 2015) reported that 9.5% of patients in the LightCycler SeptiFast Test MGRADE had an adjustment to therapy compared with 10.5% in the blood culture group. One study based on propensity score matching (Mancini et al. 2014) reported no differences in management.

4.22 One RCT (Tafelski et al. 2015) compared the LightCycler SeptiFast Test MGRADE with blood culture plus MALDI-TOF MS. Testing with the LightCycler SeptiFast Test MGRADE resulted in a change

of treatment for 9.8% of patients compared with 13.5% of patients in the blood culture plus MALDI-TOF MS group.

Mortality

4.23 Mortality data were reported in 17 studies, 12 of which reported data on a cohort level only. The mortality rates reported ranged from 4% to 61%; but the length of follow-up was highly variable across the studies. One study (Alvarez et al. 2012) reported no statistically significant differences between the LightCycler SeptiFast Test MGRADE and blood culture for both 28-day and 6-month mortality. One other study (Rodrigues et al. 2013) also reported no statistically significant difference in 28-day mortality.

4.24 One propensity score matching study (Mancini et al. 2014) reported no statistically significant difference in mortality (p=0.39) between a prospective cohort (LightCycler SeptiFast Test MGRADE) and retrospective cohort (blood culture). Although, when more stringent matching criteria were applied, the LightCycler SeptiFast Test MGRADE was associated with a statistically significant reduction in mortality (3.13% compared with 14.71%; p=0.04). A reduction in mortality associated with using the LightCycler SeptiFast Test MGRADE was reported in 2 further studies (Idelevich et al. 2015; Tafelski et al. 2015), but the reductions were not statistically significant.

SepsiTest

Mortality

4.25 One study (Loonen et al. 2014) reported a mortality rate of 3.2% for the study cohort but the duration of follow-up was not reported. In addition, Schreiber et al. (2013) reported an intensive care unit mortality rate of 16% and a 28-day mortality rate of 24% for the study cohort.

4.26 No other intermediate or clinical-outcome data were reported for the SepsiTest.

IRIDICA BAC BSI

Test-failure rates

4.27 One study, which was unpublished at the time of consultation, reported data relevant to test failure rates for the IRIDICA BAC BSI assay. These data are considered to be academic in confidence and cannot be reported at this time.

Change in antimicrobial-treatment plan

4.28 One study (Vincent et al. 2015) reported that an adjudication panel of 3 clinical experts retrospectively recommended a change in management based on the IRIDICA BAC BSI assay for 41% of all patients. This increased to 57% of patients when the IRIDICA BAC BSI assay was positive and blood culture was negative.

Mortality

4.29 Once study (Vincent et al. 2015) reported a mortality rate of 29% for the study cohort, but the duration of follow-up was not reported.

Costs and cost effectiveness

4.30 The External Assessment Group (EAG) conducted a search to identify studies investigating the cost effectiveness of the LightCycler SeptiFast Test MGRADE, SepsiTest or the IRIDICA BAC BSI assay. The EAG also constructed a de novo mathematical model to determine the cost effectiveness of the technologies.

Systematic review of cost-effectiveness evidence

4.31 Four studies were included and were assessed according to their relevance to the decision problem: 3 studies included the LightCycler SeptiFast Test MGRADE, 2 of which were within-study

cost-minimisation analyses (that is an economic evaluation conducted within a clinical study), and 1 was a cost-effectiveness analysis. The remaining study included a cost-minimisation analysis of the IRIDICA PLEX-ID hybrid assay. The target population, condition and setting varied across the 4 studies.

4.32 The 2 studies that were within-study cost-minimisation analyses of using the LightCycler SeptiFast Test MGRADE when compared with blood culture reported cost savings of €178.75 per sample (Mancini et al. 2014) and €183.00 per patient (Alvarez et al. 2012). The third study, Lehmann et al. (2010), reported incremental cost-effectiveness ratios (ICERs) of €11,477 per incremental survivor and €3,107 per quality-adjusted life year (QALY) gained when using the LightCycler SeptiFast Test MGRADE compared with blood culture. When the use of an IRIDICA-PLEX-ID hybrid system was compared with blood culture, Bilkovski et al. (2014) reported cost savings of $1,123,372 per 422 tests. None of the studies considered the effect of a potential reduction in antibiotic resistance. The EAG concluded that the existing economic evaluations had limited relevance to either the UK or the decision problem because of differences in patient populations, costs of the interventions and standard care. In particular, Mancini et al. (2014) included haematology patients for whom relatively expensive empirical antifungals were prescribed that are unlikely to be representative of the UK treatment pathway.

Economic analysis

4.33 The EAG developed a de novo conceptual mathematical model designed to explore the cost effectiveness of the LightCycler SeptiFast Test MGRADE, SepsiTest and the IRIDICA BAC BSI assay. The population included in the model was hospitalised patients with suspected bloodstream infection.

Model structure

4.34 The model comprised a decision tree with a lifetime time horizon and took the perspective of the NHS and personal social services. The key clinical outcomes included in the model were 30-day mortality, duration of stay in intensive care unit, duration of hospital stay and antimicrobial treatment.

Model inputs

4.35 Data on the diagnostic accuracy of the interventions, intermediate outcomes and clinical outcomes were taken from the clinical-effectiveness systematic review where possible. In addition, expert opinion was sought to populate key clinical outcomes and supplement the data available from the systematic review. Routine sources of costs and prevalence data were also used where appropriate. A discount rate of 3.5% per annum was applied to both costs and effects. The potential effect of the tests on antimicrobial stewardship was not included in the model, because there was insufficient evidence to show how the tests would affect antimicrobial use and the subsequent development of resistant organisms.

Costs

4.36 The incremental cost per test was calculated using the cost of the test, the net effect on duration of intensive care unit and hospital stay, and changes in the costs of antimicrobial treatment. The estimated cost per day for an intensive care unit bed was £1057 and for a general ward bed was £275. A course of empirical antimicrobial treatment was estimated to cost £350.

4.37 It was assumed that the cost per test is dependent upon both test throughput and whether laboratory equipment needs to be bought to use the tests. The range of technology costs included in the model were as follows:

- LightCycler SeptiFast Test MGRADE £153.67 to £205.54
- SepsiTest £108.30 to £149.53
- IRIDICA BAC BSI £197.35 to £314.61
- MALDI-TOF MS £6.94 to £232.39.

Health-related quality of life and QALY decrements

4.38 Incremental QALYs were calculated by assuming 11.32 discounted QALYs per 30-day mortality avoided, based on the estimated number of discounted life years for an adult patient with sepsis and the estimated quality of life after an episode of sepsis. The model assumed a mean age of 58 years and that 60% of the cohort were male. Patients were assumed to have a utility value of 0.68 at 5 years after an episode of severe sepsis (Cuthbertson et al. 2013) unless the utility value predicted for the age and sex profile of a patient in the general population was lower. In these instances, the lower utility value was applied.

Economic-analysis results

4.39 Five deterministic analyses were done:

- Base case 1: interventions compared with blood culture, with clinical-outcome data taken from the systematic review.
- Base case 2: interventions compared with blood culture, with clinical-outcome estimates taken from expert opinion.
- Threshold analyses.
- Interventions compared with MALDI-TOF MS.
- Data taken from studies comparing more than one intervention.

4.40 The following assumptions were common to all analyses:

- The only parameter to affect QALY gain or loss is 30-day mortality rate.
- Negative rapid tests do not affect any of the 4 key outcomes.
- Failed rapid tests do not affect any of the 4 key outcomes.

- If 2.4 tests per day are run, laboratories run tests Monday to Friday only, with 3 times the number of tests run on Monday to account for sample accrual over a weekend.
- If 17 or 68 tests per day are run, laboratories perform 3 runs per day and operate 24 hours a day, 7 days a week.
- The purchase cost of machines needed for the interventions and comparators is equally divided over 7 years of use.
- It was assumed that no additional staff costs or laboratory estate costs are incurred when using the interventions.
- The time scale of testing was 1 year although discounted QALYs accrued in subsequent years were included.
- Incremental QALYs were accrued through the number of avoided 30-day mortalities.
- Where accuracy data from Warhurst et al. (2015) were used, the LightCycler SeptiFast Test MGRADE has a failure rate of 6.9%. A failure rate of 1.4% was assumed when pooled accuracy data was used.
- IRIDICA BAC BSI has a failure rate of 1.9%.
- SepsiTest has a failure rate of 0%.
- Patients are treated with either 18 g per day of piperacillin/tazobactam or 3 g per day of meropenem for 7 days.
- 30-day mortality rates were assumed to be either 13% or 29%.
- MALDI-TOF MS is only used on positive samples (8.7% of all blood cultures).
- MALDI-TOF MS has a sensitivity of 79.8% at species level compared with blood culture.
- LightCycler SeptiFast test MGRADE diagnostic-accuracy data were derived from Warhurst et al. (2015) unless otherwise specified.
- SepsiTest and IRIDICA BAC BSI diagnostic-accuracy data were derived from the EAG's meta-analyses unless otherwise specified.

Base-case-1 results

4.41 In this analysis, clinical-outcome data derived from the clinical-effectiveness review were included. This resulted in the assumption that there are no clinical benefits associated with the interventions for 30-day mortality, duration of stay in the intensive care unit or duration of stay in hospital. The costs of antimicrobials were also unchanged in this analysis. All interventions were compared with blood culture only.

4.42 The results of the analysis showed that all the interventions were dominated by blood culture (that is, blood culture was less expensive and more effective than all of the interventions). Regardless of the test throughput assumed in different scenarios, the interventions remain dominated because of the lack of QALY gain.

4.43 In addition, a threshold analysis was done for base case 1 to assess the reduction in antimicrobial costs that would be needed for each intervention to be cost neutral. The results suggested that the reductions needed would be 44% to 59% for the LightCycler SeptiFast Test MGRADE, 31% to 43% for the SepsiTest and 56% to 90% for the IRIDICA BAC BSI, although the rate of positive tests associated with each intervention suggested that their costs could not be offset solely by a reduction in antimicrobial therapy use.

Base-case-2 results

4.44 In this analysis, the key clinical-outcome parameters were populated using an average of estimated values provided by clinical experts. The EAG used these values in a range of scenarios that assume a 30-day mortality rate of either 13% or 29%, a throughput of 2.4, 17 or 68 tests per day and a maximum acceptable ICER of £20,000 or £30,000 per QALY gained. The comparator used in this analysis was blood culture.

4.45 For each scenario, the net monetary benefit of each intervention was estimated. A positive net monetary benefit suggests that the benefits associated with the intervention outweigh the costs, and the intervention with the largest net monetary benefit is estimated to be the most cost effective. MALDI-TOF MS was also included in the analysis to estimate the relative cost-effectiveness between the two comparators included in the assessment.

4.46 In all scenarios modelled, MALDI-TOF MS produced a positive net benefit compared with blood culture. In one scenario (30-day mortality rate 13%, 2.4 tests per day, maximum acceptable ICER of £20,000 per QALY gained), SepsiTest had the highest net monetary benefit when it was assumed that equipment to run the test had to be bought. The IRIDICA BAC BSI assay had the highest net monetary benefit when only the test reagents and consumables were purchased. In all other modelled scenarios the IRIDICA BAC BSI assay has the highest net monetary benefit.

4.47 ICERs were also calculated using the data derived from expert opinion. When it was assumed that no additional equipment had to be bought or the 30-day mortality rate was 29%, the ICERs became more favourable because of either a reduction in incremental costs or an increase in incremental QALY gain.

4.48 In addition, the EAG explored the effect of applying the pooled estimates of sensitivity and specificity derived from the meta-analyses to the LightCycler SeptiFast Test MGRADE. This assumption produced more favourable ICERs for the LightCycler SeptiFast Test MGRADE through increasing the estimated sensitivity of the test (65% pooled estimate compared with 51% from Warhurst et al. 2015), while maintaining specificity at 86%.

Threshold analyses

4.49 The EAG used a range of threshold analyses to explore the effect of key clinical outcomes. In all analyses, it was assumed that the comparator equipment had already been bought but that the equipment for the interventions needed to be bought. The threshold levels resulting from the analyses, which assume 2.4 tests run per day and a maximum acceptable ICER of £20,000 per QALY gained, suggested reductions in 30-day mortalities ranging from 0.09 to 0.14 per 100 tests would be needed for the interventions to be considered cost effective compared with blood culture. Antimicrobial costs would need to reduce by £149.53 to £314.61 per 100 tests. The results were similar when the interventions were compared with MALDI-TOF MS. The threshold analyses that assumed either 17 or 68 tests run per day produced lower threshold values. In addition, the values of the reductions needed were lower when a maximum acceptable ICER of £30,000 per QALY gained was assumed.

Cost effectiveness of the LightCycler SeptiFast Test MGRADE and SepsiTest compared with MALDI-TOF MS

4.50 The EAG also explored the cost effectiveness of both the LightCycler SeptiFast Test MGRADE and SepsiTest compared with MALDI-TOF MS, based on data from 2 studies (Tafelski et al. 2015; Loonen et al. 2014) that used MALDI-TOF MS in addition to blood culture. The effect estimates based on expert opinion were also included in the analysis. It was assumed that both interventions had a failure rate of 0% and that equipment to run the tests needed to be bought. The results of these analyses suggested that when compared with MALDI-TOF MS (and blood culture), the LightCycler SeptiFast Test MGRADE dominates MALDI-TOF MS (and blood culture), and SepsiTest has ICERs ranging from £23,375 to £34,848 per QALY gained with a 30-day mortality rate of 13% and

from £10,479 to £15,621 per QALY gained with a 30-day mortality rate of 29%.

Results from studies comparing the LightCycler SeptiFast Test MGRADE and SepsiTest simultaneously with blood culture

4.51 An analysis was run using data from 2 studies (Schreiber et al. 2013; Leitner et al. 2013), which evaluated both the LightCycler SeptiFast Test MGRADE and SepsiTest with blood culture. The analysis was done to compare the relative cost-effectiveness estimates with those derived in base case 2 that were based on indirect comparisons of the relative effectiveness of the interventions from expert opinion. The analysis assumed a 0% test-failure rate for both interventions and that equipment to run the tests needed to be bought. A range of scenarios were presented with 30-day mortality rates of 13% or 29% and a throughput of 2.4, 17 or 68 tests per day. In all scenarios the ICER for the LightCycler SeptiFast Test MGRADE was greater than £30,000 per QALY gained when compared with SepsiTest.

5 Considerations

5.1 The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of using the LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay to rapidly identify bloodstream bacteria and fungi in people with a suspected bloodstream infection.

Clinical effectiveness

5.2 The Committee considered the evidence for the diagnostic accuracy of each of the rapid molecular tests compared with blood culture. It noted that 54 studies reported data for the LightCycler SeptiFast Test MGRADE, 6 of which included children or neonates, 4 reported data for SepsiTest and 4 reported data for the IRIDICA BAC BSI assay. The Committee noted that most of the included

studies were considered to have unclear risks of bias, particularly about details of the reference standard and the populations included in the studies. The Committee considered that the unclear risk of bias was attributable to poor reporting in the studies, and concluded that it was not possible to adequately assess the quality of the studies included in the diagnostic accuracy meta-analyses.

5.3 The Committee noted that 2 studies compared either the LightCycler SeptiFast Test MGRADE or SepsiTest with MALDI-TOF mass spectrometry. The Committee therefore concluded that there was insufficient evidence to establish either the diagnostic accuracy or the clinical utility of the rapid molecular tests against this comparator.

5.4 The Committee questioned the assumption in the diagnostic accuracy meta-analyses that blood culture is 100% accurate. It heard from the External Assessment Group (EAG) that it was possible that the pooled estimates of sensitivity and specificity had been underestimated in the analysis. Further, it heard from clinical specialists that it is possible that the rapid molecular tests may provide more accurate results in some scenarios, such as the detection of fastidious organisms that may not grow in culture. The Committee concluded that although the sensitivity and specificity may have been underestimated in the meta-analyses, the absence of data on the clinical significance of discordant results means that the size of any underestimation cannot be determined.

5.5 The Committee discussed the prevalence of positive blood cultures in both the included diagnostic accuracy studies and clinical practice. It heard from clinical specialists that blood culture is often negative in practice, with only around 10% of blood cultures being positive. The Committee considered that the low prevalence of positive blood cultures was likely to mean that there would be a

relatively low number of false negative rapid molecular test results in routine practice. Conversely, the absolute rate of false-positive rapid molecular test results is likely to be high because of the greater prevalence of negative blood cultures. The Committee concluded that although the absolute number of false-negative rapid molecular test results was likely to be low in practice, the consequences of changing antimicrobial treatment in this group could be severe.

5.6 The Committee discussed the studies included in the clinical-outcomes systematic review. It noted that fewer studies reported clinical-outcome data compared with diagnostic-accuracy data, and that studies typically reported data for the LightCycler SeptiFast Test MGRADE only. The Committee noted that most of the studies were done in Europe or the USA and questioned the applicability of the clinical-outcome studies to the UK. It heard from clinical specialists that although the treatment of sepsis is based on international guidelines, clinical outcomes such as duration of intensive care unit stay and duration of antimicrobial therapy cannot usually be extrapolated to the UK from international studies because of differences in antibiotic prescribing practices. The Committee concluded that although the included studies provide some indication of the likely effect of the rapid molecular tests on clinical outcomes, additional UK-based studies are needed to show the clinical utility of the tests in practice.

5.7 The Committee considered the test turnaround times reported by the studies and heard from clinical specialists that the shorter times seen in research studies are unlikely to be replicated in routine clinical practice, unless a molecular service is available 24 hours a day. It noted that 24-hour services may become available if microbiology laboratories are joined into networks or centralised, but that this was unlikely to happen in the very near future. The

Committee also noted that in some studies, the reported test-failure rates for the LightCycler SeptiFast Test MGRADE were high (up to 24.2%) and considered that this could further affect its potential to rapidly deliver information for clinical decision-making. The Committee concluded that faster reporting of results is highly dependent on laboratory infrastructure and that the turnaround times needed to gain benefits from the rapid molecular tests are unlikely to be achieved in routine practice.

5.8 The Committee considered the data for mortality and duration of intensive care unit or hospital stay and noted that the studies were unlikely to have had sufficient power to detect significant differences for these clinical endpoints. The Committee also noted that most of the studies did not report statistically significant differences between the rapid molecular tests and standard practice. Further, it heard from clinical specialists that both mortality and duration of stay among people with suspected bloodstream infection are likely to be influenced by multiple factors, and that any differences are unlikely to be solely attributable to the use of a rapid molecular test. The Committee therefore concluded that mortality and duration of stay may not be appropriate primary clinical outcomes for studies, and suggested that future studies should consider using change in antimicrobial prescribing as a surrogate clinical outcome.

5.9 The Committee discussed the plausibility of the rapid molecular tests having an effect on antimicrobial prescribing. It noted that the results of the clinical-effectiveness analysis suggested that only small numbers of people, if any, would have changes made to their antimicrobial treatment plan. The Committee heard from clinical specialists that there may be some situations where the rapid molecular tests could affect patient management. Further, it heard that these situations would be restricted to instances where the

rapid test was positive, because the current accuracy of the tests was not sufficient to convince clinicians to withdraw antibiotic therapy on the basis of a negative test result. The Committee concluded that although the rapid molecular tests might provide results more quickly, it was unlikely that the information they provide would have an effect on patients' treatment plans and antimicrobial prescribing at present.

Cost effectiveness

5.10 The Committee discussed the results of the economic analyses and questioned whether the use of an imperfect reference standard to derive the estimates of diagnostic accuracy for the rapid molecular tests could have introduced bias. The Committee heard from the EAG that negative results were assumed not to have an effect on outcomes and that false-positive results were associated with benefits in the model. The Committee concluded that any underestimate of pooled diagnostic accuracy in the clinical-effectiveness analysis is unlikely to have a substantial effect on the results of the economic model.

5.11 The Committee questioned the assumptions made about the number of tests processed per day. It heard from clinical experts that the estimates based on 68 tests per day were unrealistic and that a large service laboratory would be unlikely to receive more than 40 blood cultures per day. The Committee noted that the EAG had also produced estimates based on 2.4 and 17 tests per day. The Committee heard from the EAG that 68 tests per day was included as an extreme scenario to show the effect on the results of the economic analyses. The Committee concluded that the most representative scenarios in the economic analyses were those that assumed either 2.4 or 17 tests per day.

5.12 The Committee discussed the differences in the results produced in the 2 different base cases of the economic analyses. It noted that the main difference between the 2 base cases arose from the difference in data source for clinical outcomes: base case 1 used data taken from the systematic review, whereas base case 2 used data based on expert opinion. The Committee noted that the systematic review suggested that the rapid molecular tests had no effect on clinical outcomes, but some of the clinical experts thought that the tests may be beneficial, although their estimates of the magnitude of the benefit varied widely. The Committee therefore concluded that the tests may offer clinical benefit, but there is too much uncertainty in the size of the benefit to determine the effect of introducing the tests into clinical practice. The Committee also noted that the incremental cost-effectiveness ratios (ICERs) in base case 2 ranged from the rapid molecular tests being more costly and equally effective (dominated) than blood culture, to being less costly and more effective (dominant) than blood culture alone, when using estimates from individual clinicians. The Committee considered that the wide range of ICERs resulted from the high level of variation between the clinicians' estimates. The Committee therefore concluded that the effect of introducing the rapid molecular tests on NHS resources was highly uncertain and that consequently the results of the economic analyses were subject to substantial uncertainty.

5.13 The Committee considered the likely effect of the costs and outcomes that had been excluded from the economic analyses and noted that these included laboratory overhead and staff costs and clinical benefits, which may be accrued through improved antimicrobial stewardship. The Committee noted that because the results of the clinical-effectiveness analysis suggested that the effect of the rapid molecular tests on antimicrobial prescribing was highly uncertain, it would have been inappropriate to extrapolate

the clinical outcomes to estimate an effect on antimicrobial stewardship. Further, it noted that the rapid molecular tests would most likely increase laboratory overhead costs, and possibly staff costs, and concluded that in view of the clinical uncertainties their omission from the economic analyses was unlikely to have a substantial effect.

5.14 The Committee considered the results of the threshold analyses and noted the reductions in antimicrobial costs that would be needed for the tests to be considered cost effective. The Committee noted that this ranged from £823.34 to £1482.28 per 100 positive tests, depending on whether the rapid molecular tests were compared with blood culture or blood culture plus MALDI-TOF mass spectrometry. The Committee concluded that in view of the prevalence of positive tests in clinical practice, the costs of the rapid molecular tests were unlikely to be offset by reduced antimicrobial costs alone.

5.15 The Committee noted that the economic analyses did not include neonates and children, and that the model was based on an adult population with a mean age of 58 years. The Committee considered that the estimated quality-adjusted life year (QALY) gain through avoided 30-day mortalities would be greater for children and neonates because of their relatively greater number of life years remaining, but accepted that there was insufficient clinical-utility data for this population for an economic analysis.

Additional considerations

5.16 The Committee considered the potential benefits of the interventions in practice. It heard from clinical experts that because the tests can be used directly on whole blood samples, they may be able to give information on a pathogen's identity earlier in the care pathway than tests that need incubated blood samples or

samples from culture plates, which could be beneficial for antimicrobial stewardship. Further, it heard that the information from the rapid molecular tests may be used to modify a person's antimicrobial therapy, particularly when empirical antimicrobial therapy has been prescribed. The Committee concluded that 1 of the key claimed benefits of the rapid molecular tests is their potential to contribute towards antimicrobial stewardship.

5.17 The Committee considered that because the rapid molecular tests need to be used in addition to blood culture for antimicrobial susceptibility testing, they may be less suitable for use in neonates and children. The Committee heard from clinical experts that this is a particular issue for tests that need a large volume of whole blood. In addition, the Committee heard from clinical specialists that using a lower volume of blood from these patients for the molecular tests may have an adverse effect on the test's sensitivity and concluded that further exploration of these analytical issues should be encouraged.

Research considerations

5.18 The Committee discussed the value of developing research recommendations for the rapid molecular tests. The Committee considered that for the tests to have clinical utility in both research settings and routine practice, clinicians would need to be certain that the tests are sufficiently accurate, and be confident that basing antimicrobial prescribing decisions on the results of the tests would not lead to adverse outcomes for people. The Committee noted that the reported accuracy data from the systematic review were unlikely to be sufficient for clinical decision-making at present. The Committee concluded that further research is needed to determine the clinical scenarios in which the tests may offer most benefit in clinical decision-making and to quantify their clinical utility.

5.19 The Committee considered that, conceptually, the molecular tests show promise for the early identification of fungal pathogens in people who are thought to be at increased risk of developing invasive fungal infections. The Committee concluded that if the accuracy of the tests was sufficient to guide clinical decision-making in this population, they could offer substantial value and address a clinically unmet need. The Committee encouraged future studies in this population and highlighted that the studies should aim to quantify the clinical utility of the rapid molecular tests, including their effect on antifungal prescribing. The Committee noted that studies planned by the NIHR Health Technology Assessment Programme may investigate the use of rapid tests for identifying fungal pathogens.

5.20 The Committee considered the utility of further research to quantify the levels of certainty about the results of rapid molecular tests, which clinicians need to decide to change treatment and level of care for patients. It noted that the results of an elicitation exercise could be used to guide the development of future diagnostic tests, which are designed to be used to change treatment plans for patients who are acutely unwell; the Committee encourages this research.

5.21 The Committee considered that because an increasing number of microbiology laboratories are adopting MALDI-TOF mass spectrometry for rapidly identifying bloodstream bacteria and fungi, future studies aiming to establish the clinical utility of rapid molecular tests should include this technology as a comparator where possible.

5.22 The Committee noted that there was insufficient evidence to determine whether the tests were clinically effective in children and neonates. It wished to encourage the inclusion of these populations

in future research studies, and noted that particular consideration should be given to establishing whether the blood volumes needed for the tests are suitable for these populations.

6 Related NICE guidance

Published

- Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. NICE guideline 15 (2015)
- Antibiotics for neonatal infection. NICE quality standard 75 (2014)
- Faecal microbiota transplant for recurrent Clostridium difficile infection. NICE interventional procedure guidance 485 (2014)
- Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults. NICE clinical guideline 191 (2014)
- Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. NICE clinical guideline 169 (2013)
- Feverish illness in children: Assessment and initial management in children younger than 5 years. NICE clinical guideline 160 (2013)
- Intravenous fluid therapy in adults in hospital. NICE clinical guideline 174 (2013)
- Surgical site infection. NICE quality standard 49 (2013)
- Antibiotics for early-onset neonatal infection: Antibiotics for the prevention and treatment of early-onset neonatal infection. NICE clinical guideline 149 (2012)
- Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. NICE clinical guideline 151 (2012)
- Prevention and control of healthcare-associated infections: Quality improvement guide. NICE public health guidance 36 (2011)
- Bacterial meningitis and meningococcal septicaemia: Management of bacterial meningitis and meningococcal septicaemia in children and young

people younger than 16 years in primary and secondary care. NICE clinical guideline 102 (2010)

- Diarrhoea and vomiting in children: Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years. NICE clinical guideline 84 (2009)
- Rehabilitation after critical illness. NICE clinical guideline 83 (2009)
- Surgical site infection: Prevention and treatment of surgical site infection. NICE clinical guideline 74 (2008)
- Acutely ill patients in hospital: Recognition of and response to acute illness in adults in hospital. NICE clinical guideline 50 (2007)
- Urinary tract infection in children: Diagnosis, treatment and long-term management. NICE clinical guideline 54 (2007)

Under development

NICE is developing the following guidance (details available from the NICE website):

- Procalcitonin testing for diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay). NICE diagnostics guidance. Publication expected October 2015.
- Intravenous fluids therapy in children. NICE clinical guideline. Publication expected December 2015
- Antimicrobial stewardship – changing risk-related behaviours in the general population. NICE public health guidance. Publication expected March 2016.
- Sepsis. NICE clinical guideline. Publication expected July 2016.
- Acute medical emergencies in adults and young people, service guidance. NICE clinical guideline. Publication expected November 2016.

7 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland
Chair, Diagnostics Advisory Committee
September 2015

8 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Adrian Newland
Chair, Diagnostics Advisory Committee

Dr Mark Kroese
Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst
Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Dr Phil Chambers
Research Fellow, Leeds Institute of Cancer and Pathology, University of Leeds

Dr Sue Crawford
GP Principal, Chillington Health Centre

Professor Erika Denton
National Clinical Director for Diagnostics, NHS England; Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards
Head of Health Technology Assessment, BMJ Evidence Centre

Mr David Evans

Lay member

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Mr John Hitchman

Lay member

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Mr Matthew Lowry

Director of Finance and Infrastructure, Doncaster and Bassetlaw Hospitals NHS Foundation Trust

Dr Michael Messenger

Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

Dr Peter Naylor

GP, Chair Wirral Health Commissioning Consortia

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Ms Gail Norbury

Consultant Clinical Scientist, Guy's and St Thomas' NHS Foundation Trust

Dr Simon Richards

Vice President of Regulatory Affairs, EME, Alere Inc

Dr Deirdre Ryan

Consultant Cellular Pathologist, Royal London Hospital

Professor Mark Sculpher

Professor of Health Economics, Centre for Health Economics, University of York

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger

Chief Executive Officer, DiaSolve Ltd, London

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, St Thomas' Hospital

Specialist Committee members

Dr Andrew Bentley

Consultant in Intensive Care and Respiratory Medicine, University Hospital of South Manchester

Ms Julie Crawford

Lay member

Dr Jim Gray

Consultant Microbiologist, Birmingham Children's Hospital

Dr Bob Phillips

Senior Clinical Academic and Honorary Consultant in Paediatric and Adolescent Oncology, Leeds Teaching Hospital NHS Trust

Dr Cassie Pope

Consultant Clinical Scientist, St George's University Hospitals NHS Foundation Trust

Dr Muhammad Raza

Consultant Microbiologist and Virologist, Newcastle Hospitals NHS Trust

Mr Suman Shrestha

Advanced Critical Care Nurse Practitioner, Frimley Park Hospital NHS Trust

NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Rebecca Albrow
Topic Lead

Dr Sarah Byron
Technical Adviser

Robert Fernley
Project Manager

9 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by the School of Health and Related Research (ScHARR), University of Sheffield.

- Stevenson M, Pandor A, Martyn-St James M et al. Sepsis: The LightCycler SeptiFast Test MGRADE, SepsiTest and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi. A systematic review and economic evaluation. July 2015.

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- Abbott Laboratories
- Roche Diagnostics
- Molzym

Other commercial organisations:

- Alacrita LLP
- Anagnostics
- Hain Lifescience UK Ltd

Professional groups and patient/carer groups:

- Group B Strep Support
- UK Sepsis Trust

Research groups:

None

Associated guideline groups:

- National Clinical Guidelines Centre

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government