NICE advice

eazyplex SuperBug kits for detecting carbapenemase-producing organisms

Medtech innovation briefing
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Summary

- The **technologies** described in this briefing are the eazyplex SuperBug kits (complete A, complete B and CRE). They are used with the Genie II platform to detect carbapenemase-producing organisms (CPOs) and selected extended-spectrum beta-lactamase (ESBL) genes in rectal swab samples.
- The **innovative aspects** are that they are molecular diagnostic tests to detect bacterial DNA in up to 30 minutes, and can identify major types of carbapenemases.
- The intended **place in therapy** would be instead of the first stage culture-based tests currently used to detect CPOs, but antimicrobial-resistance testing would still be needed for CPO-positive samples.

- The **key points from the evidence** summarised in this briefing are from 4 studies (1 comparative diagnostic performance study, 2 diagnostic performance studies and 1 proof-of-concept study) including a total of 721 samples. One study reported that the sensitivity and specificity of the SuperBug complete A were 95.5% and 100% respectively. One study reported 100% agreement between the eazyplex SuperBug CRE system and laboratory sequencing results for clinical isolates. One study reported that the sensitivity and specificity of the SuperBug CRE test were 100% and 97.9% respectively, for the detection of the ESBL genes in urine samples.
- **Key uncertainties** around the evidence are that none of the studies evaluated the kits as they are intended to be used in clinical practice, because they did not test rectal swab samples. It is also limited to data generated from diagnostic performance studies conducted in vitro with no data on clinical outcomes for patients.
- The **cost** of the eazyplex kits is £755 for 24 single-use tests and the Genie II system costs £9,000 (exclusive of VAT). These are more expensive than standard culture-based tests (about £7 per test) and would therefore carry additional acquisition costs.
- NICE has also published a medtech innovation briefing on the Xpert Carba-R test to identify people carrying CPOs.

The technology

The eazyplex SuperBug kits are qualitative in vitro diagnostic tests to detect bacteria that carry genes for the production of carbapenemases and selected extended-spectrum beta-lactamases (ESBL).

These kits would be used to determine the presence of carbapenemase-producing organisms (CPOs) and ESBL genes in people when colonisation with these organisms is suspected. These are Gram-negative bacteria that are usually resistant to carbapenems, the 'drugs of last resort' for many bacterial infections. They include enterobacteriaceae and non-fermenting bacteria which have acquired genes that make carbapenemases, enzymes that break down the carbapenem class of antibiotics. However, many of these carbapenemase enzymes can also cause resistance or reduced susceptibility to all or most members of the beta-lactam class of antibiotics (Public Health England 2016). Detection of ESBL genes can also identify possible resistance to the extended-spectrum cephalosporin class of antibiotics.

Three types of eazyplex SuperBug test kit are available, each with different ranges of gene

variants: SuperBug complete A, SuperBug complete B and SuperBug CRE (carbapenem-resistant enterobacteriaceae), as described in table 1. The choice of these kits is likely to depend on sample type, risk group, and the geographic and epidemiological situation.

Table 1 The eazyplex SuperBug kits and gene variant ranges

Gene or gene variants	SuperBug complete A	SuperBug complete B	SuperBug CRE
Carbapenemases			
KPC-2 to -15	Yes	Yes	Yes
NDM-1 to -7	Yes	Yes	Yes
OXA-48 group (including OXA-48, -162, -204, -244)	Yes	Yes	Yes
OXA-23 group (including OXA-23, -27, -48, -73)	Yes	Yes	No
OXA-40 group (including OXA-24, -25, -26, -40, -72)	Yes	Yes	No
OXA-181/-232	No	Yes	Yes
OXA-58 group (including OXA-58, -96, -97)	Yes	No	No
VIM-1 to -37	Yes	Yes	Yes
Extended-spectrum beta-lactamases			
CTX-M-1-group	No	No	Yes
CTX-M-9-group	No	No	Yes

The eazyplex SuperBug kits consist of 8-microtube test strips containing freeze-dried, ready-to-use reagents for the amplification of 7 resistance genes and 1 internal control. They are used with the Genie II platform to carry out loop-mediated isothermal amplification (LAMP) of carbapenemase-encoding genes and ESBL-encoding genes. The platform is a mains- or battery-powered instrument, which uses a single channel fluorescence excitation and detection system. It can hold two 8-microtube test strips that can be processed independently or together.

The Genie III and Genie HT platforms are currently being developed for use with the eazyplex test kits. The Genie III is a smaller hand-held device for one 8-microtube test strip, whereas the Genie HT can process up to twelve 8-microtube test strips independently.

The SuperBug complete A and complete B kits test rectal swab samples taken with eSwab CE480 (Copan) or bacterial isolates from agar plates. However, the sample material for the SuperBug CRE kit can be bacterial isolates from agar plates, blood culture media from positive flagged blood culture bottles, rectal swabs taken with the eSwab, or urine.

Samples are suspended in the resuspension and lysis fluid (RALF) buffer solution (supplied with the kit) and incubated for 2 minutes for thermal lysis, according to the manufacturer's instructions for use. For each reaction, 25 microlitres of the bacteria-RALF-solution is transferred to the 8-microtube strip using a pipette. The test strip is then immediately placed into the Genie II device and the amplification process is started. The test run can be monitored in real-time mode on the user interface and results are ready in up to 30 minutes. Positive results are shown by a strong rise in fluorescence signal and different colours are given to each of the tested gene variants. The test run is invalid if the result of the inhibition control is coloured red.

The company also supplies a range of eazyplex kits for 5 other in vitro diagnostic tests, including the Colistin resistance gene mcr-1 (eazyplex SuperBug mcr-1), methicillin-resistant Staphylococcus aureus (eazyplex MRSA), Clostridium difficile (eazyplex C. difficile), vancomycin-resistant enterococci (eazyplex VRE), and cerebrospinal fluid (eazyplex CSF direct). These tests are beyond the scope of this briefing.

The innovation

CPOs are typically detected using microbiological culturing techniques which can take between 24 and 48 hours to give a result. Culturing techniques cannot usually differentiate between different carbapenemases and ESBL types.

The eazyplex SuperBug kits and the Genie II platform are molecular diagnostic systems, which use LAMP to detect and identify carbapenemase- and selected ESBL-encoding genes in rectal swab samples within 30 minutes. They would give results faster than the first stage of standard microbiological culturing used to identify CPO colonisation and would also provide more information about the type of carbapenemase present.

Current NHS pathway or current care pathway

People known to have been colonised before, or who are at risk of colonisation with CPOs, are routinely tested during hospital admission. If they test positive, they should immediately be isolated according to the Public Health England Acute Trust Toolkit (Public Health England 2013). Some hospitals may also test patient groups for organisms beyond those covered in the toolkit.

The Acute Trust Toolkit recommends testing 3 stool samples or rectal swabs collected on days 0, 2 and 4 after admission (Public Health England 2013). However, guidelines from a joint working party on the prevention and control of multi-drug-resistant Gram-negative bacteria recommend a single screening swab on admission (Wilson et al. 2016).

The samples are often tested for CPO colonisation by microbiological culturing using a selective (chromogenic) medium. This process of culture and incubation and getting a result typically takes 24 hours for positive samples and 48 hours for negative samples. If any CPO colonies are detected, additional tests are needed to determine the type of carbapenem resistance (Public Health England 2013). This would involve antimicrobial susceptibility testing using microbiological agar plates and an indicator carbapenem. If a sample is considered resistant to the carbapenem, further supplementary tests are done to distinguish carbapenemase producers from those that have other carbapenem-resistance mechanisms. Confirmatory tests can be inhibitor-based in which synergy can be shown between the indicator carbapenem and various carbapenemase inhibitors. Other methods include the modified Hodge test, the Carba-NP test (bioMerieux, US) or polymerase chain reaction (PCR)-based assays (Public Health England 2016).

The following samples should also be sent to the Reference Laboratory at Public Health England for further testing, to assess outbreaks:

- all enterobacteriaceae suspected of producing a carbapenemase
- all *Pseudomonas* species suspected of producing a carbapenemase
- all *Acinetobacter* species suspected of producing a metallo-carbapenemase.

The eazyplex SuperBug kits would be used in place of standard culture-based tests to determine the presence or absence of CPOs, although supplementary and confirmatory tests such as antimicrobial-resistance testing may still be needed for CPO-positive samples. Using these kits could result in a quicker diagnosis of CPO colonisation (in rectal

swabs) or infection (from other specimen types) and allow healthcare providers to implement local infection control protocols to prevent transmission to other susceptible people. This could also allow CPO carriage to be more quickly excluded, so that people do not have to wait so long to be released from isolation.

NICE is aware of the following CE-marked devices that fulfil a similar function as the eazyplex SuperBug kits:

- Xpert Carba-R (Cepheid)
- Check-Direct CPE/Check-Direct EBSL (Check-Points).

NICE has also published a medtech innovation briefing on the Xpert Carba-R test.

Population, setting and intended user

The eazyplex SuperBug kits would be used on rectal swab samples from people who are at high risk of, or who are suspected of, colonisation with CPOs. The SuperBug CRE kit can also be used with other specimen types. They would be used in secondary or tertiary care clinical laboratories and run by qualified laboratory staff with appropriate training on the test and system.

Costs

Device costs

A half to full day of training is provided when the system is first installed, as part of the purchase cost.

The basic warranty for the Genie II instrument is for 1 year. There are no parts in the Genie II instrument that need regular maintenance. However, performance of the optical components can be affected by general wear and tear and debris collected over time. The company recommends that the instrument should be returned for servicing at least once every 2 years, depending on usage.

Table 2 Current costs of the eazyplex SuperBug test components

Description	Cost (excluding VAT)	Additional information
eazyplex SuperBug complete A, complete B, or CRE	£755	Contains 24 single-use test kits and all the consumables needed to do the test (excluding eSwabs).
eazyplex SuperBug complete A, complete B, or CRE including eSwabs	£1,542	Contains 48 single-use test kits, 50 eSwabs and all the consumables needed to do the test.
Genie II instrument	£9,000	Includes 150 W mains power adaptor, power cable, USB cable, PC software and internal rechargeable battery. Price includes Amplex software, barcode wand, printer and set-up blocks.
Extended warranty for the Genie II instrument	£2,500	One-off payment to extend the warranty to a total of 5 years. Includes a single service when needed and unlimited repairs or replacements within the warranty period.
Servicing	£750	For each service.

Costs of standard care

Recommended care first involves microbiological culturing of rectal or stool samples on admission and immediately isolating the patient. Further testing would include confirmatory testing of carbapenem-resistant mechanisms and antimicrobial susceptibility testing.

The national average unit cost of a microbiological test is £7 (£4 to £9) according to the National schedule of reference costs for 2014/15.

Resource consequences

Individual eazyplex SuperBug kits and the Genie II system are considerably more expensive than current microbiological culture techniques and would therefore represent an additional acquisition cost to the NHS. There will also be costs associated with maintenance, training and quality assurance.

However, the faster turnaround time and greater level of information provided could lead to more efficient use of isolation resources by excluding CPO carriage quicker, therefore avoiding prolonged time in isolation. Quicker detection of CPO carriage may also result in faster infection control implementation and more appropriate antimicrobial therapy. Four specialist commentators advised that limited training would be needed and 1 suggested that the technology could be used in the laboratory by staff from any discipline or grade.

Regulatory information

The eazyplex SuperBug kits are CE marked as in vitro diagnostic devices. The company, Amplex, has current CE certification dated August 2016 which includes the following eazyplex SuperBug kits:

- SuperBug complete A (CE marked in November 2013)
- SuperBug complete B (CE marked in July 2014)
- SuperBug CRE (CE marked in August 2013).

A search of the Medicines and Healthcare products Regulatory Agency website revealed that no manufacturer Field Safety Notices or Medical Device Alerts have been issued for this technology.

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).

No equality considerations were identified for this technology.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published 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

Four studies are summarised in this briefing: 1 comparative diagnostic performance study (Findlay et al. 2015), 2 diagnostic performance studies (Vergara et al. 2014; Garcia-Fernandez et al. 2015) and 1 proof-of-concept study (Hinic et al. 2015).

Table 3 summarises the clinical evidence as well as its strengths and limitations.

Strengths and limitations of the evidence

The available evidence on using the eazyplex SuperBug kits is currently limited to diagnostic performance studies. These studies did not evaluate diagnostic performance in a clinical setting, nor did they compare performance with an appropriate reference standard used in healthcare practice (microbiological culture). No studies were identified that reported clinical or healthcare-related outcomes.

Three studies used clinical bacterial isolates and 1 study used urine samples, which is not representative of current clinical practice that uses rectal or stool samples to detect carbapenemase-producing organisms (CPOs). The diagnostic performance results may therefore not be generalisable.

One specialist commentator highlighted that all of the studies assessed samples with a relatively high inoculum of bacteria. This raises questions about the assay's sensitivity when low inocula are present and when it is more difficult to concentrate the inoculum of

CPOs from faecal material. They considered that for successful screening of rectal swabs, clinicians will need to be confident that low inocula can be detected and that faecal material is not interfering with assay performance.

Table 3 Summary of evidence

Study size, design and location	Intervention and comparators	Outcomes	Strengths and limitations
Findlay et al. (2015) n=450 clinical isolates from various bacterial species Comparative diagnostic performance study UK	The eazyplex SuperBug complete A kit, Xpert Carba-R and Check-Direct CPE (on 2 different platforms). These were compared with a reference standard using PCR assays and a commercial microarray (Check-MDR CT102).	The overall test sensitivity and specificity were 95.5% and 100% respectively. The eazyplex SuperBug A was unable to detect 18% (18/102) OXA-48 variant carbapenemase genes. A modified eazyplex SuperBug complete B kit was later provided and correctly identified the 18 OXA-181 producers.	A large panel of bacterial isolates were used, with carbapenemase-resistance mechanisms defined through appropriate methods. The distribution of the carbapenemases seen in this study did not mimic the natural distribution of carbapenemases because of the selection of isolates for carbapenemase diversity. No results other than the OXA-181 were reported for the eazyplex SuperBug complete B kit.

Vergara et al. (2014) n=82 clinical isolates from *Acinetobacter* species Diagnostic performance study Spain	The eazyplex SuperBug complete A kit (not explicitly stated but identified based on the range of carbapenemase genes). The presence of genes encoding carbapenemases was confirmed by PCR and DNA sequencing.	The presence or absence of carbapenem-hydrolysing enzymes was correctly determined for all isolates except IMP2 and OXA-51, which are not detected by the eazyplex SuperBug complete A test. Unspecific DNA amplification was seen for 5 samples in the KPC, OXA-58 and OXA-40 reaction tubes, which accounted for false-positive results.	The study was limited to only *Acinetobacter baumannii* strains of bacteria. No sensitivity or specificity results were reported.

Garcia-Fernandez et al. (2015) N=94 genotypically characterised carbapenemase-producing strains and 45 clinical isolates Diagnostic performance study Spain (2 centres)	The eazyplex SuperBug CRE kit with the GENIE II platform. Conventional PCR assays and sequencing were used to characterise carbapenemase genes in the carbapenemase-producing strains. Identification of the carbapenemases in the clinical isolates was done by minimum inhibitory concentration profiles and the modified Hodge test. Double-disc synergy tests were done for ESBL identification.	There was 100% agreement between the eazyplex SuperBug CRE system results and the PCR and sequencing results. For the contemporary isolates, 100% concordant results were found between the inferred phenotype and the eazyplex SuperBug CRE system results. Cycle threshold values for the genes detected ranged from 3 minutes 45 seconds to 9 minutes 45 seconds.	A range of different micro-organisms was identified from both the carbapenemase-producing strains and the contemporary clinical isolates. There were no clinical isolates expressing more than 1 carbapenemase simultaneously. However, co-expressions of ESBLs and carbapenemases were identified. The study was done in Spain and so the distribution of the carbapenemases seen in this study may not mimic the distribution of carbapenemases in the UK.

Hinic et al. (2015) n=50 urine samples (including 35 corresponding bacterial isolates) Proof-of-concept study Switzerland	The eazyplex SuperBug CRE kit with the GENIE II platform. Phenotypic confirmation of ESBL production on culture isolates was done with Etest ESBL and AmpC strips (bioMerieux).	The eazyplex test correctly identified CTX-M-1- and CTX-M-9-group-encoding genes in all 30 urine samples with confirmed ESBL production (sensitivity 100%). One out of 48 urine samples tested had a false-positive result (specificity 97.9%). Two urine samples gave invalid results because of multiple unspecific fluorescent signals. The analytical sensitivity for testing with the newly developed urine protocol was between 102 and 103 CFU/ml.	The study only investigated the detection of ESBL-encoding genes. Results for the identification of carbapenemase-encoding genes and of co-expression with ESBL-encoding genes were tabulated but not discussed. No sensitivity or specificity values were reported for these.
Abbreviations: CFU, colony forming units; ESBL, extended-spectrum spectrum beta-lactamases; PCR, polymerase chain reaction.			

Recent and ongoing studies

No ongoing or in-development trials were identified.

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and

relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

One of the 5 specialist commentators has used this technology as part of an evaluation study.

Level of innovation

Two specialist commentators noted that several kits are available for detecting carbapenemase-producing organisms (CPOs) and 1 considered that the eazyplex SuperBug kits are only a minor variation on these technologies. However, 2 specialist commentators described the use of loop-mediated isothermal amplification in this application as innovative and 1 added that this makes it faster than other polymerase chain reaction based tests.

Potential patient impact

Four of the specialist commentators considered that quicker identification of people with CPOs would allow more appropriate antimicrobial therapy. Broad spectrum antibiotic use in people with negative results may be avoided, whereas optimised antimicrobial therapy could be used in people with positive results. One specialist commentator advised that detection of CPOs in rectal swabs only indicates colonisation which may not need antibiotic therapy. Therapy should only be considered if CPOs are detected in a clinically significant specimen type, which is possible using the SuperBug CRE kit.

All 5 specialist commentators suggested that quicker identification of people with CPOs would also improve infection control. Being able to rule out CPOs would avoid the need to treat the person in isolation, so that they would have a better healthcare experience. One commentator added that faster rule-out may also prevent people being refused admission to long-term residential care or transfer to other hospitals.

One specialist commentator considered that people with positive results would also benefit from better infection control regarding planning of surgery and avoidance of urinary catheterisation.

Potential system impact

One specialist commentator highlighted that the technology could be used by laboratory staff of any discipline or grade, and it is possible to do the testing at any time of the day. One commentator advised that the Genie II platform is very small so takes up little space in the laboratory, however 1 other indicated that space and staff resources would be needed to run the test in the laboratory.

One specialist commentator highlighted that the real benefit of this test would be in getting a negative result, which could allow patients to be released from isolation at an earlier stage, so freeing up a limited resource and resulting in significant cost savings. Two specialist commentators also suggested that using these tests could reduce the risk of transmission of CPOs to other people.

Two specialist commentators did not consider that the tests would result in cost savings because they are significantly more expensive than current practice. However, 2 commentators considered that there could be overall cost savings because of the early release of patients from isolation facilities, despite the greater direct costs to the laboratories. One considered that the prevalence of CPOs would need to be above 2% for this to happen. They also considered that the higher test cost would have to be offset by the reduced risk of CPO transmission, which would in turn depend on isolation room availability in the first instance.

General comments

Three commentators considered that the major limitation of these tests is that their diagnostic accuracy with rectal swab samples has not been evaluated. Two also highlighted that no evidence is currently available to show that a single eazyplex SuperBug test has the same sensitivity as 3 successive culture tests. However, they thought that it was plausible that the eazyplex SuperBug tests could be more sensitive than culture.

One specialist commentator considered that the SuperBug complete A kit would be more suitable for testing cultures than rectal swabs, because OXA-58 variants are associated with Acinetobacter, a hospital-acquired pathogen. However, 1 commentator also noted that the absence of the OXA-181/-232 variant in the SuperBug complete A kit reduces its effectiveness especially in the UK.

One specialist commentator also identified patients' refusal to have rectal swabs as a

possible limitation of the eazyplex SuperBug kits, and considered that the technology may need to include stool samples as potential test material.

Two specialist commentators highlighted that CTX enzymes are the most common extended-spectrum beta-lactamases (ESBLs) found in E. coli, and are therefore the most common ESBL circulating outside hospitals. They considered that finding a positive result for these isolates in people in hospital might prompt different infection control, in which patients who would not typically be isolated are isolated. Another added that this could cause problems if patients with positive results were to be isolated, which would block single rooms needed for patients with higher priority pathogens.

Specialist commentators

The following clinicians and other specialist experts contributed to this briefing:

- Dr Jim Gray, Consultant Microbiologist, Birmingham Children's Hospital NHS Foundation Trust (also Editor-in-Chief of the Journal of Hospital Infection, and a Council Member and Trustee of the Healthcare Infection Society)
- Professor John Perry, Clinical Scientist, Newcastle upon Tyne Hospitals NHS Foundation Trust (has received funding for research or royalty payments from diagnostics companies, including bioMerieux and Lab M, which market competing products to eazyplex SuperBug kits)
- Allison Sykes, Practice Development Lead Infection Prevention and Control, Newcastle upon Tyne Hospitals NHS Foundation Trust (no conflicts of interest reported)
- Professor Peter Wilson, Consultant Microbiologist, University College London Hospitals NHS Foundation Trust (no conflicts of interest reported)
- Professor Neil Woodford, Consultant Clinical Scientist and Head of the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, Public Health England (has evaluated many commercial kits for detecting carbapenemases; has received funding and free materials from several diagnostics companies [including Amplex] for Public Health England initiated and independent contract evaluations).

Development of this briefing

This briefing was developed for NICE by the Newcastle and York External Assessment Centre. 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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