Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER357
Topic:	T2 Magnetic Resonance to aid early diagnosis of sepsis
Summary of findings:	T2 Magnetic Resonance (T2MR) uses a combination of nuclear magnetic resonance and polymerase chain reaction (PCR) assays to directly detect sepsis-causing bacteria and candida. Three assays are available: T2Bacteria, T2Candida and T2Resistance. We identified a 2016 Technology Brief from the Adelaide Health Technology Assessment (AHTA) unit on rapid sepsis detection using T2MR, including the T2Candida panel. The authors concluded that T2Candida test reported good sensitivity and specificity, however, given the low incidence of candida septicaemia, it is unlikely to be cost-effective. We also identified one systematic review and nine observational studies investigating use of either T2Candida or T2Bacteria. The systematic review and meta-analysis evaluated healthcare utilisation, including time to results, length of stay and mortality. Based on pooled data from one randomised controlled trial and nine observational studies, there was no difference in mortality between T2MR and blood culture. However, time to result (species identification, targeted therapy, de-escalation of therapy), length of ICU stay and length of hospital stay were shorter with T2MR than blood culture. Most of the primary studies that we identified were prospective, with patient numbers ranging from 20 to 1,427 participants. Outcomes included detection rates, diagnostic accuracy (i.e. sensitivity and specificity), time to results and healthcare utilisation. Two of the studies reported downstream clinical outcomes, such as change in management or mortality. The largest study (n = 1,427) reported both sensitivity and specificity as 90% for proven blood stream infections. The systematic review did not include economic evidence in its literature review. However, the authors did note three potentially relevant economic studies. Two of the studies evaluate rapid diagnostic tests; it is not clear from the systematic review if these are T2MR tests specifically. The remaining study reported that testing with T2Candida would be cost saving.

Introduction and aims

Sepsis, sometimes called septicaemia or blood poisoning, is where the immune system overreacts to an infection and starts to damage the tissue and organs. It is often life-threatening and can be challenging to diagnose. People with sepsis can experience vague symptoms that often relate to other conditions, such as common viral infections.

T2 magnetic resonance (T2MR) is designed to aid the early diagnosis of sepsis in people who are critically ill, specifically:

- Adults in intensive care with suspected sepsis or septic shock
- Newborns in intensive care with suspected sepsis or failure to thrive
- People with neutropenia in critical care
- People with transplants
- Oncology patients

T2MR combines nuclear magnetic resonance and polymerase chain reaction (PCR) assays to directly detect blood stream infections from sepsis-causing bacteria and candida. There are currently three different panels available to use: T2Bacteria panel, T2Candida panel and T2Resistance panel (the resistance panel detects genes for antibiotic resistance). The manufacturer state all three T2MR panels have CE mark class I (or IVDD general category, or IVDR class A) regulatory status.

Health Technology Wales researchers searched for evidence on magnetic resonance assays to diagnose sepsis.

Evidence overview

Guidelines

The National Institute for Health and Care Excellence (NICE) have published two guidelines on sepsis (NICE guideline 51) and neutropenic sepsis in people with cancer (NICE guideline 151). NICE recommends that management of people with suspected sepsis is stratified based on risk criteria. For people who meet one or more high risk criteria, or two or more moderate to high risk criteria, management includes undertaking venous blood tests, including blood culture. For adults and young people aged 12 years and over who meet one or more high risk criteria, broad-spectrum antimicrobials at the maximum recommended dose should be given without delay. The guidelines to not mention use of T2MR assays.

Health technology assessments and publications

We identified a 2016 Technology Brief from the Adelaide Health Technology Assessment (AHTA) unit on rapid sepsis detection using either the T2Candida panel, or polymerase chain reaction/electrospray ionization-mass spectrometry technology (trade name IRIDICA)(Ellery, 2016). The authors concluded that T2Candida test has good sensitivity and specificity, however, given the low incidence of candida septicaemia, it is unlikely to be cost-effective. These conclusions were based on low to intermediate level evidence and the report noted that further investigation, namely randomised controlled trials to capture outcomes such as change in patient management, would be beneficial.

Systematic reviews and meta-analyses

We identified one systematic review and meta-analysis comparing antimicrobial and resource utilisation with T2MR (using either the T2Bacteria or the T2Candida panels) versus blood culture, in people with suspected bloodstream infection (Giannella et al. 2021). Outcomes evaluated included time to detection, time to species identification, time to targeted therapy (for positive cases), time to empirical therapy de-escalation (for negative cases), length of ICU stay, length of hospitalisation, and mortality. The authors pooled relevant data from one randomised controlled trial, nine prospective controlled observational studies, and four retrospective observational studies. No difference was observed in mortality rates between T2MR and blood culture (28.9% vs. 29.9%, risk ratio [RR] = 1.02). Time to detection and time to species identification were significantly faster with T2MR (median difference [MD] -81 hours and -77 hours, respectively), as was time to targeted therapy (MD -42 hours) and to a lesser extent time to de-escalated empirical therapy (MD -7 hours). Length of stay was shorter with T2MR than blood culture for both ICU (MD -5.0 days) and hospital stays (-4.8 days).

Primary evidence

We identified nine primary studies investigating use of T2MR; five studies included the T2Candida panel, three included the T2Bacteria panel and one study included both. The majority (8/9) studies were prospective cohort studies and sample sizes ranged from 30 to 1,427 participants. Reported outcomes included detection rates (7/9 studies), concordance/agreement with standard blood culture (4/9 studies), diagnostic accuracy (i.e. sensitivity and specificity, 4/9 studies) and time to result (3/9 studies). Two studies explored downstream clinical outcomes (change in management and/or mortality). Overall, studies concluded that T2MR could provide an accurate and timely diagnosis. The largest study (n = 1,427) aimed to assess the performance of the T2Bacteria panel in cases of suspected bloodstream infection or sepsis; sensitivity and specificity for proven bloodstream infections were 90% and 90%, respectively.

Economic evidence

The systematic review we identified did not include economic analyses in their review (Giannella et al. 2021). However, the authors refer to three economic studies. The first reported savings of 27,000 USD per patient for testing with the T2Candida panel. The remaining two studies evaluate rapid diagnostic tests; however, it is not clear from the systematic review if these are T2MR tests specifically.

Areas of uncertainty

This exploration focused on diagnostic tests that used PCR with magnetic resonance. If this were to proceed to fuller appraisal, consideration should be given on whether the scope of assessment should include other types on other novel PCR-based diagnostics or rapid diagnostics for sepsis. Some examples of other rapid diagnostic tests include FA-BCID panel, Prove-it Sepsis, VYOO, SepsiTest, Magicplex sepsis real-time, LightCycler SeptiFast assay.

The meta-analysis reported above pooled outcomes from both the T2Bacteria and T2Candida panels; it is unclear whether panels are similar enough that pooling evidence from the two different panels is appropriate. It is also unclear whether one or both tests would be implemented within the service; HTW would need to consider which panels are relevant to assess should this process to fuller appraisal.

Although economic evidence has been identified, it is unclear whether the evidence would be appropriate to adapt or build upon as part of a de novo economic analysis.

Fuller appraisal of the evidence would be required to determine the study setting, e.g. in emergency units, and their relevance for pathways in Wales. Should an appraisal focus on more specific settings, this may reduce the pool of relevant or appropriate evidence.

Literature search results

Health technology assessments and guidance
Ellery, Parsons. (2016). Rapid sepsis detection. Adelaide Health Technology Assessment (AHTA). Available at: https://www.coaghealthcouncil.gov.au/Portals/0/HealthPACT/Rapid%20sepsis%20detection_Technology%20Brief_December%202016.pdf. NICE. (2012). Neutropenic sepsis: prevention and management in people with cancer. Clinical guideline [CG151]. Available at: https://www.nice.org.uk/guidance/cg151 NICE. (2017). Sepsis: recognition, diagnosis and early management. NICE guideline [NG51]. Available at: https://www.nice.org.uk/guidance/ng51.
Evidence reviews and economic evaluations
Giannella M, Pankey GA, Pascale R, et al. (2021). Antimicrobial and resource utilization with T2 magnetic resonance for rapid diagnosis of bloodstream infections: systematic review with meta-analysis of controlled studies. Expert Rev Med Devices. 18(5): 473-82.
Individual studies
Clancy CJ, Pappas PG, Vazquez J, et al. (2018). Detecting Infections Rapidly and Easily for Candidemia Trial, Part 2 (DIRECT2): A Prospective, Multicenter Study of the T2Candida Panel. Clin Infect Dis. 66(11): 1678-86. doi: 10.1093/cid/cix1095 De Angelis G, Posteraro B, De Carolis E, et al. (2018). T2Bacteria magnetic resonance assay for the rapid detection of ESKAPEc pathogens directly in whole blood. J Antimicrob Chemother. 73(suppl_4): iv20-iv6. doi: 10.1093/jac/dky049 Giannella M, Paolucci M, Roncarati G, et al. (2018). Potential role of T2Candida in the management of empirical antifungal treatment in patients at high risk of candidaemia: a pilot single-centre study. J Antimicrob Chemother. 73(10): 2856-9. doi: 10.1093/jac/dky247 Kalligeros M, Zacharioudakis IM, Tansarli GS, et al. (2020). In-depth analysis of T2Bacteria positive results in patients with concurrent negative blood culture: a case series. BMC Infect Dis. 20(1): 326. doi: 10.1186/s12879-020-05049-9 Munoz P, Vena A, Machado M, et al. (2018). T2Candida MR as a predictor of outcome in patients with suspected invasive candidiasis starting empirical antifungal treatment: a prospective pilot study. J Antimicrob Chemother. 73(suppl_4): iv6-iv12. doi: 10.1093/jac/dky047 Nguyen MH, Clancy CJ, Pasculle AW, et al. (2019). Performance of the T2Bacteria Panel for Diagnosing Bloodstream Infections: A Diagnostic Accuracy Study. Ann Intern Med. 170(12): 845-52. doi: 10.7326/M18-2772 Quirino A, Scaglione V, Marascio N, et al. (2022). Role of the T2Dx magnetic resonance assay in patients with suspected bloodstream infection: a single-centre real-world experience. BMC Infectious Diseases. 22(1): 113. Muñoz P, Vena A, Machado M, et al. (2018). T2MR contributes to the very early diagnosis of complicated candidaemia. A prospective study. Journal of Antimicrobial Chemotherapy. 73(suppl_4): iv13-iv9. doi: 10.1093/jac/dky048 Mylonakis E, Zacharioudakis IM, Clancy CJ, et al. (2018). Efficacy of T2 Magnetic Resonance Assay in Monitoring Candidemia after Initiation of Antifungal Therapy: the Serial Therapeutic and Antifungal Monitoring Protocol (STAMP) Trial. Journal of Clinical Microbiology. 56(4): e01756-17. doi: doi:10.1128/JCM.01756-17
Ongoing research
We did not identify any ongoing research for this topic.

Date of search:	April 2022
Concepts used:	Sepsis, magnetic resonance, T2MR, T2bacteria, T2Candida

(Internal use only – delete before publication)

Proposed research question and evidence selection criteria

Proposed research question	**What is the clinical and cost effectiveness of T2 magnetic resonance to aid the diagnosis of sepsis?**

	Included	Excluded
Population	People who are critically ill with suspected sepsis *Settings: emergency/acute care, ICU,NICU?*	
Intervention	T2 Magnetic Resonance (T2MR) *Both panels?*	*Other rapid diagnostic tests for suspected sepsis?*
Reference standard	Post-blood culture species identification	
Comparison/ comparators	Standard care (blood culture)	
Outcomes	Diagnostic accuracy Mortality Change in management Healthcare utilisation	
Study design	*Likely to rely on observational diagnostic studies*	

Topic selection criteria:

Criteria		Comments
Are there likely to be sufficient published research findings available upon which to base a technology assessment, and to allow HTW to provide clear advice to support decision making?	**Yes**	Assuming we are happy to focus on both panels (and the approach of pooling evidence for both, taken by the SR)
Is a clear additional health benefit to patients or benefit to the NHS anticipated or evident from the use of this technology?	**Yes**	Appears to be a potential benefit with quicker turnaround time than standard cultures.
Is there wide variation in provision or outcome of the technology across NHS Wales, and/or uncertainty about the effectiveness of the technology?	**Unclear**	Appears to be some centres in England using T2Candida. Unclear how prevalent this usage is, or whether there has been Welsh usage

Is the technology likely to have an impact on NHS resources (consuming or releasing)?	**Yes**	Shows potential of reducing healthcare utilisation. HTC form says approx. £220 for test. A cost study reported savings of 27,000 USD per patient (although not delved into the included costs behind this figure). The SR also suggests cost saving of 10,000 to 25,000 USD per patient (based on hospital costs for sepsis patients at 2,000-5,000 a day).
Is the technology likely to have a major impact on NHS Wales?	**Yes**	Based on initial exploration, due to the potential of saving time and reducing hospital stay.
Is there potential for quality improvement from undertaking an assessment of this technology at this time?	**Yes**	As above