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:

1. Inform discussions on new topics received by HTW.
2. Determine the quantity and type of evidence available on a topic.
3. Assess the topic against HTW selection criteria.

Topic:	Synovasure alpha defensin test for use in the diagnosis of periprosthetic joint infection
Topic exploration report number	TER015
Referrer:	Jeff Stonadge, Zimmer Biomet
Topic exploration undertaken by:	Health Technology Wales

Aim of Search

Health Technology Wales researchers searched for evidence on whether the Synovasure test for Periprosthetic Joint Infection (PJI) improves PJI diagnosis when included in a PJI diagnostic protocol.

Summary of Findings

The Scottish Health Technologies Group published an Innovative Medical Technology Overview in December 2017 entitled Synovasure® Alpha Defensin Lateral Flow Test Kit (IMTO 009/2017). The IMTO concluded that Synovasure shows promising preliminary results, but that further testing and evaluation is required. The search in this topic exploration concentrated on articles published since the IMTO was published.

The Second International Consensus Meeting (ICM) on PJI was held in Philadelphia in July 2018. Recommendations from the Musculoskeletal Infection Society (MSIS) were reviewed and voted upon. This included a vote which agreed to the use of an alpha-defensin test to complement existing diagnostic tests. The references for this recommendation are included at the end of this report.

Seven references are common to both the IMTO and ICM Philadelphia reports. The former has three unique references and the latter twelve, four of which were published in 2018.

Two additional systematic reviews on Synovasure were located (Ahmad et al 2018 and Marson et al 2018) as well as three which discuss alpha-defensin and PJI (Jun & Jianghua 2018, Mitchell et al 2017 and Saleh et al 2017). Furthermore, five primary studies on Synovasure (de Saint-Vincent et al, Okroi et al, Plate et al, Riccio et al and Scholten et al) and seven on alpha-defensin and PJI (Kelly et al, Parvizi et al, Shohat et al, Sigmund et al, Stone et al, Tahta et al, and Tarabichi et al) have been published in 2018.

Both Ahmad et al and Marson et al compare the Synovasure POCT with Synovasure laboratory based tests for alpha-defensin and conclude that the Synovasure lateral flow test is less effective. Ahmad et al also say that the Synovasure test should be critically appreciated, while Marson et al state that 'further studies are required before widespread adoption of the lateral flow cassette'.

Jun & Jianghua and Mitchell et al both conclude that alpha-defensin may be more efficient than PCR (polymerase chain reaction) and help improve accuracy in diagnosing PJI. Saleh et al all states that alpha-defensin has a high diagnostic utility.

The primary studies on Synovasure conclude that while the low risk of a false negative result means that you can reliably rule out PJI (Plate et al, de Saint Vincent et al), the false positive result risk is higher, so the test cannot be used on its own (Okroi et al, Plate et al, Riccio et al). Scholten et al found that the intraoperative exclusion of PJI using the test during revision surgery was more limited than previously indicated.

The primary studies on alpha-defensin and PJI are varied. Parvizi et al provide an evidence-based definition for diagnosing hip and knee PJI. Shohat et al and Tahta et al both conclude that inflammatory joint diseases do not affect the accuracy of alpha-defensin testing. Sigmund et al conclude that there is no difference between the qualitative and quantitative alpha-defensin test for confirmation of PJI, and that the advantage of providing results within 10 minutes means that the qualitative test may be of interest in the intraoperative setting, despite the higher test expense. Both Kelly et al and Stone et al find that the alpha-defensin test is prone to false positives (especially if there is a underlying additional factor such as recent antibiotic use), while Tarabichi et al discuss next generation sequencing.

Conclusions

Synovasure has been appraised by SHTG in the form of an IMTO in 2017. This search has identified the existence of new evidence published subsequent to the IMTO that could be included in any appraisal by HTW, and a review of this evidence (along with any included in the IMTO) would be needed to fully inform any guidance issued by HTW.

Areas of Uncertainty

It is unclear whether Synovasure would be used as an addition to, or replacement for, current PJI diagnostic tools. It is also unclear which tests are included in a 'standard' diagnostic protocol.

There appears to be uncertainty around which groups of people, or types of evidence, should be excluded from any appraisal by HTW.

Feasibility of Technology Assessment

HTW's Assessment Group concluded to progress this topic to Evidence Appraisal following clearer definition of the PICO (population, intervention, comparison, outcome). HTW's appraisal will be published as EAR008 – please refer to this for the final agreed inclusion criteria for evidence.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland:	IMTO 009/2017 on 'Synovasure® Alpha Defensin Lateral Flow Test Kit' was published in December 2017. http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_imto/imto_009-2017.aspx Key references used in the report: • *Balato, G., et al. (2018). "High performance of alpha-defensin lateral flow assay (Synovasure) in the diagnosis of chronic knee prosthetic infections." Knee Surgery, Sports Traumatology, Arthroscopy 26(6): 1717-1722. • *Berger, P., et al. (2017). "Diagnosis of prosthetic joint infection with alpha-defensin using a lateral flow device: a multicentre study." Bone & Joint Journal 99-B(9): 1176-1182. • *Bonanzinga, T., et al. (2017). "How Reliable Is the Alpha-defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection? A Prospective Study." Clinical Orthopaedics & Related Research 475(2): 408-415. • Deirmengian, C., et al. (2015). "The Alpha-defensin Test for Periprosthetic Joint Infection Responds to a Wide Spectrum of Organisms." Clinical Orthopaedics & Related Research 473(7): 2229-2235. • *Kasparek, M. F., et al. (2016). "Intraoperative Diagnosis of Periprosthetic Joint Infection Using a Novel Alpha-Defensin Lateral Flow Assay." Journal of Arthroplasty 31(12): 2871-2874. • *Shahi, A., et al. (2016). "The Alpha-defensin Test for Periprosthetic Joint Infections Is Not Affected by Prior Antibiotic Administration." Clinical Orthopaedics & Related Research 474(7): 1610-1615. • *Sigmund, I. K., et al. (2017). "Qualitative alpha-defensin test (Synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty." Bone & Joint Journal 99-B(1): 66-72. • *Suda, A. J., et al. (2017). "Diagnosis of periprosthetic joint infection using alpha-defensin test or multiplex-PCR: ideal diagnostic test still not found." International Orthopaedics 41(7): 1307-1313. • Wyatt, M. C., et al. (2016). "The Alpha-Defensin Immunoassay and Leukocyte Esterase Colorimetric Strip Test for the Diagnosis of Periprosthetic Infection: A Systematic Review and Meta-Analysis." Journal of Bone & Joint Surgery - American Volume 98(12): 992-1000. • Xie, K., et al. (2017). "Procalcitonin and alpha-Defensin for Diagnosis of Periprosthetic Joint Infections." Journal of Arthroplasty 32(4): 1387-1394. *Note*: References marked with * were also references used to inform ICM Philadelphia (see last section in table).
Health Technology Assessment Group	We did not find any relevant health technology assessments on the use of lateral flow testing for PJI.
Health Information and Quality Authority	We did not find any relevant health technology assessments on the use of lateral flow testing for PJI.
UK guidelines and guidance	
SIGN	We did not find any relevant guidelines on the use of lateral flow testing for PJI.

NICE	We did not find any relevant guidelines or guidance on the use of lateral flow testing for PJI.

Secondary literature and economic evaluations	
ECRI	• ECRI Institute. Next-generation Sequencing for Diagnosing Prosthetic Joint Infection. Plymouth Meeting (PA): ECRI Institute; 2017 Oct 31. (Custom Rapid Responses). https://www.ecri.org/components/Hotline/Pages/25553.aspx#
Cochrane library	We did not find any relevant secondary evidence on the use of lateral flow testing for PJI.
Medline	**Synovasure:** • Ahmad, S. S., et al. (2018). "A meta-analysis of synovial biomarkers in periprosthetic joint infection: SynovasureTM is less effective than the ELISA-based alpha-defensin test." Knee Surgery, Sports Traumatology, Arthroscopy 26(10): 3039-3047. • Marson, B. A., et al. (2018). "Alpha-defensin and the Synovasure lateral flow device for the diagnosis of prosthetic joint infection." Bone & Joint Journal 100-B(6): 703-711. **Alpha-defensin & PJI:** • Clauss, M. (2018). "CORR Insights: Does the Alpha-defensin Immunoassay or the Lateral Flow Test Have Better Diagnostic Value for Periprosthetic Joint Infection? A Systematic Review." Clinical Orthopaedics & Related Research 476(5): 1073-1075. • Eriksson, H., et al. (2018). "Erratum to: Does the Alpha-defensin Immunoassay or the Lateral Flow Test Have Better Diagnostic Value for Periprosthetic Joint Infection? A Systematic Review." Clinical Orthopaedics & Related Research 476(7): 1545. • Jun, Y. and L. Jianghua (2018). "Diagnosis of Periprosthetic Joint Infection Using Polymerase Chain Reaction: An Updated Systematic Review and Meta-Analysis." Surgical Infections 19(6): 555-565. • Mitchell, D., et al. (2017). "Systematic Review of Novel Synovial Fluid Markers and Polymerase Chain Reaction in the Diagnosis of Prosthetic Joint Infection." American Journal of Orthopedics (Chatham, Nj) 46(4): 190-198. • Saleh, A., et al. (2017). "The Diagnostic Utility of Synovial Fluid Markers in Periprosthetic Joint Infection: A Systematic Review and Meta-analysis." Journal of the American Academy of Orthopaedic Surgeons 25(11): 763-772.
Primary studies	
Medline	**Synovasure:** • de Saint Vincent, B., et al. (2018). "Diagnostic accuracy of the alpha defensin lateral flow device (Synovasure) for periprosthetic infections in microbiologically complex situations: A study of 42 cases in a French referral centre." Orthopaedics & traumatology, surgery & research 104(4): 427-431. • Okroj, K. T., et al. (2018). "The Alpha-Defensin Test for Diagnosing Periprosthetic Joint Infection in the Setting of an Adverse Local Tissue Reaction Secondary to a Failed Metal-on-Metal Bearing or Corrosion at the Head-Neck Junction." Journal of Arthroplasty 33(6): 1896-1898.

	• Plate, A., et al. (2018). "Inflammatory disorders mimicking periprosthetic joint infections may result in false positive alpha-defensin." Clinical Microbiology & Infection 26: 26. • Riccio, G., et al. (2018). "Qualitative Alpha-defensin Versus The Main Available Tests For The Diagnosis Of Periprosthetic Joint Infection: Best Predictor Test?" Journal Of Bone And Joint Infection 3(3): 156-164. • Scholten, R., et al. (2018). "Low sensitivity of a-defensin (Synovasure) test for intra-operative exclusion of prosthetic joint infection." Acta Orthopaedica 89(3): 357-359. **Alpha-defensin & PJI:** • Ehrlich, G. D. and M. P. Palmer (2018). "High-Fidelity Point-of-Care Diagnostic Test for Periprosthetic Joint Infection: Commentary on an article by Thorsten Gehrke, MD, et al.: "The Accuracy of the Alpha Defensin Lateral Flow Device for Diagnosis of Periprosthetic Joint Infection. Comparison with a Gold Standard"." Journal of Bone & Joint Surgery - American Volume 100(1): e7. • Fillerova, R., et al. (2017). "Excellent Diagnostic Characteristics for Ultrafast Gene Profiling of DEFA1-IL1B-LTF in Detection of Prosthetic Joint Infections." Journal of Clinical Microbiology 55(9): 2686-2697. • Goswami, K., et al. (2018). "Current Recommendations for the Diagnosis of Acute and Chronic PJI for Hip and Knee-Cell Counts, Alpha-Defensin, Leukocyte Esterase, Next-generation Sequencing." Current reviews in musculoskeletal medicine 11(3): 428-438. • Kelly, M. P., et al. (2018). "Synovial Fluid Alpha-Defensin Is an Adjunctive Tool in the Equivocal Diagnosis of Periprosthetic Joint Infection." Journal of Arthroplasty 33(11): 3537-3540. • Parvizi, J., et al. (2018). "The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria." Journal of Arthroplasty 33(5): 1309-1314.e1302. • Shohat, N., et al. (2018). "Diagnosing Periprosthetic Joint Infection in Inflammatory Arthritis: Assumption Is the Enemy of True Understanding." Journal of Arthroplasty 33(11): 3561-3566. • Sigmund, I. K., et al. (2018). "Is the Enzyme-linked Immunosorbent Assay More Accurate Than the Lateral Flow Alpha Defensin Test for Diagnosing Periprosthetic Joint Infection?" Clinical Orthopaedics & Related Research 476(8): 1645-1654.
Cochrane library	We did not find any relevant primary evidence on the use of lateral flow testing for PJI.
Ongoing secondary research	
PROSPERO database	**Synovasure:** Both records found, Marson and Suen, have been published – papers are listed in Medline systematic reviews search and ICM Philadelphia references, respectively. **Alpha-defensin & PJI:** • Sigismondo Luca Di Donato, Giovanni Balato, Massimo Mariconda, Andrea Baldini. Quantitative vs qualitative assessment of alpha-defensin in periprosthetic joint infection: a systematic review and meta-analysis. PROSPERO 2017 CRD42017077276 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017077276

	• Susan Goodman, Serene Mirza, Shawn Richardson, Cynthia Kahlenberg, Jason Blevins, Jackie Szymonifka, Peter Sculco, Mark Figgie. Diagnosing prosthetic joint infection in patients with inflammatory arthritis using synovial biomarkers. PROSPERO 2018 CRD42018085973 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018085973
Ongoing primary research	
Clinicaltrials.gov	**Synovasure:** • Clinical Validation of CD Diagnostics Synovasure PJI ELISA Test and Synovasure PJI Lateral Flow Test for Detection of Periprosthetic Joint Infection in Synovial Fluid NCT02868736 https://clinicaltrials.gov/ct2/show/NCT02868736?term=synovasure&rank=1 **Alpha-defensin & PJI:** • Arthrocentesis Study NCT02530229 https://clinicaltrials.gov/ct2/show/NCT02530229?term=periprosthetic+and+defensin&rank=1 • Diagnosis of Periprosthetic Joint Infection and the Common Pathogens, Drug-resistance in Periprosthetic Joint Infection NCT03365323 https://clinicaltrials.gov/ct2/show/NCT03365323?term=%22periprosthetic+joint+infection%22&rank=1 • The Utility of Next-generation Sequencing for the Diagnosis of Periprosthetic Joint Infection NCT03200470 https://clinicaltrials.gov/ct2/show/NCT03200470?term=%22periprosthetic+joint+infection%22&rank=7 • Rapid Diagnosis of Prosthetic Joint Infection by Matrix-assisted Laser Desorption NCT03717090 https://clinicaltrials.gov/ct2/show/NCT03717090?term=%22periprosthetic+joint+infection%22&rank=13
Other	
Evidence identified by topic proposer	The Second International Consensus meeting on PJI was held in Jefferson University, Philadelphia on 25-27 July 2018. See link for the hip and knee Q&A document. Pages 295-300 are relevant to alpha-defensin. https://icmphilly.com/document/icm-2018-hip-and-knee-document/ (click on 'Hip & Knee questions and answers' to access the document as a pdf) **References from the relevant section:** • *Balato, G., et al. (2018). "High performance of alpha-defensin lateral flow assay (Synovasure) in the diagnosis of chronic knee prosthetic infections." Knee Surgery, Sports Traumatology, Arthroscopy 26(6): 1717-1722. • *Berger, P., et al. (2017). "Diagnosis of prosthetic joint infection with alpha-defensin using a lateral flow device: a multicentre study." Bone & Joint Journal 99-B(9): 1176-1182. • Bingham, J., et al. (2014). "The alpha defensin-1 biomarker assay can be used to evaluate the potentially infected total joint arthroplasty." Clinical Orthopaedics & Related Research 472(12): 4006-4009. • *Bonanzinga, T., et al. (2017). "How Reliable Is the Alpha-defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection? A Prospective Study." Clinical Orthopaedics & Related Research 475(2): 408-415.

- Deirmengian, C., et al. (2015). "The alpha-defensin test for periprosthetic joint infection outperforms the leukocyte esterase test strip." Clinical Orthopaedics & Related Research 473(1): 198-203.
- Deirmengian, C., et al. (2014). "Combined measurement of synovial fluid alpha-Defensin and C-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection." Journal of Bone & Joint Surgery - American Volume 96(17): 1439-1445.
- Eriksson, H. K., et al. (2018). "Does the Alpha-defensin Immunoassay or the Lateral Flow Test Have Better Diagnostic Value for Periprosthetic Joint Infection? A Systematic Review." Clinical Orthopaedics & Related Research 476(5): 1065-1072.
- Frangiamore, S. J., et al. (2016). "alpha-Defensin Accuracy to Diagnose Periprosthetic Joint Infection-Best Available Test?" Journal of Arthroplasty 31(2): 456-460.
- Gehrke, T., et al. (2018). "The Accuracy of the Alpha Defensin Lateral Flow Device for Diagnosis of Periprosthetic Joint Infection: Comparison with a Gold Standard." Journal of Bone & Joint Surgery - American Volume 100(1): 42-48.
- Kanwar, S., et al. (2018). "What Is the Optimal Criteria to Use for Detecting Periprosthetic Joint Infections Before Total Joint Arthroplasty?" Journal of Arthroplasty 33(7S): S201-S204.
- *Kasparek, M. F., et al. (2016). "Intraoperative Diagnosis of Periprosthetic Joint Infection Using a Novel Alpha-Defensin Lateral Flow Assay." Journal of Arthroplasty 31(12): 2871-2874.
- Lee, Y. S., et al. (2017). "Synovial Fluid Biomarkers for the Diagnosis of Periprosthetic Joint Infection: A Systematic Review and Meta-Analysis." Journal of Bone & Joint Surgery - American Volume 99(24): 2077-2084.
- Li, B., et al. (2017). "Synovial Fluid alpha-Defensin as a Biomarker for Peri-Prosthetic Joint Infection: A Systematic Review and Meta-Analysis." Surgical Infections 18(6): 702-710.
- Renz, N., et al. (2018). "Alpha Defensin Lateral Flow Test for Diagnosis of Periprosthetic Joint Infection: Not a Screening but a Confirmatory Test." Journal of Bone & Joint Surgery - American Volume 100(9): 742-750.
- *Shahi, A., et al. (2016). "The Alpha-defensin Test for Periprosthetic Joint Infections Is Not Affected by Prior Antibiotic Administration." Clinical Orthopaedics & Related Research 474(7): 1610-1615.
- *Sigmund, I. K., et al. (2017). "Qualitative alpha-defensin test (Synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty." Bone & Joint Journal 99-B(1): 66-72.
- *Suda, A. J., et al. (2017). "Diagnosis of periprosthetic joint infection using alpha-defensin test or multiplex-PCR: ideal diagnostic test still not found." International Orthopaedics 41(7): 1307-1313
- Suen, K., et al. (2018). "Synovasure 'quick test' is not as accurate as the laboratory-based alpha-defensin immunoassay: a systematic review and meta-analysis." Bone & Joint Journal 100-B(1): 66-72.
- Yuan, J., et al. (2017). "Diagnostic accuracy of alpha-defensin in periprosthetic joint infection: a systematic review and meta-analysis." International Orthopaedics 41(12): 2447-2455.

Note: References marked with a * were also references used to inform IMTO 009/2017 by SHTG.

Date of search:	24 October 2018
Concepts used:	Synovasure; alpha-defensin and periprosthetic joint infection (and relevant synonyms)