Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 008 (June 2019)

Synovasure® Alpha Defensin Test for diagnosing Periprosthetic Joint Infection

HTW guidance: The use of Synovasure® alpha defensin testing shows promise in the diagnosis of peri-prosthetic hip and knee infection but the evidence does not currently support routine adoption. Synovasure® has the potential to further the diagnosis in patients with equivocal results from conventional testing but more convincing evidence is needed. HTW therefore recommends further research in this group of patients to define diagnostic accuracy, clinical outcomes and cost consequences of the use of synovasure® in addition to standard investigations.

Why did Health Technology Wales (HTW) appraise this topic?

This topic was referred to HTW by the manufacturer of the Synovasure® alpha defensin test (Zimmer Biomet). Periprosthetic Joint Infection (PJI) is an uncommon but serious complication of hip and knee replacement surgery, affecting approximately 1% of hip arthroplasties and 1% to 2% of knee arthroplasties. PJI is difficult to diagnose and the use of the Synovasure® alpha defensin test may improve detection rates and ultimately result in more appropriate patient management.

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Appraisal Panel considerations

- The Appraisal Panel recognised that although peri-prosthetic joint infection is a relatively rare complication of hip and knee replacement surgery, the condition is often difficult to diagnose and the clinical consequences can be grave. In view of the importance of clinical decision-making that includes the possible need for re-operation, the Panel considered that there is a clinical need to optimize the current diagnostic pathway and that the use of Synovasure® alpha defensin testing in addition to clinical assessment and conventional testing offers the potential to do so.
- The Panel noted that Synovasure® measures the level of alpha defensin in synovial fluid and can be done as a laboratory test or as a point-of care (POC) test. It was informed that the company is planning to offer the laboratory test as part of a a package of tests reflecting the range of parameters included in the agreed diagnostic criteria. It was concluded that the different modes of testing is likely to be applicable to different clinical scenarios and that the value proposition of each therefore needs to be considered separately.
- The Panel learnt from experts that the diagnosis of peri-prosthetic hip or knee infection can be reliably established in the majority (approximately 80%) of patients through the use of well-defined and validated clinical and laboratory testing criteria. The Panel concluded that while the evidence shows high levels of diagnostic accuracy with laboratory Synovasure® testing when compared with these criteria, no clinical outcome studies are currently available to determine the consequences of the use of laboratory Synovasure® testing on clinical management decisions. It concluded that, on the basis of the current evidence, the added clinical value of routine laboratory testing with laboratory Synovasure® in this manner is uncertain and cannot currently be supported.
- The Panel learnt from experts that in the minority of patients (approximately 20%) where the outcome of clinical assessment and laboratory testing leads to equivocal conclusions about the presence or absence of peri-prosthetic hip or knee joint infection, there is a need for additional diagnostic refinement. The Panel concluded that it is in this group of patients that the use of Synovasure® testing may be of particular added clinical value. The Panel noted a single prospective non-randomized study (De St Vincent et al) that was done in 39 patients with equivocal conventional testing in which the point-of-care Synovasure® was associated with high levels of sensitivity (88.9%), specificity (90.6%) and negative predictive value (94.4%) for peri-prosthetic joint infection. The Panel concluded that while the results of this study are encouraging, further evidence, including clinical outcomes, is needed to promote the routine adoption of POC Synovasure® testing in this clinical scenario.
- The economic analysis showed that the routine use of laboratory Synovasure® testing in possible peri-prosthetic joint infection was not cost effective either for hip or knee replacements. The use of POC Synovasure® testing in the context of equivocal outcomes from clinical and laboratory assessments was estimated to be cost effective in the context of possible peri-prosthetic knee infection (ICER of £16,273 per QALY) but not in the context of possible hip infection (ICER of £47,688 per QALY). The Panel noted, however, that in view of the limited clinical evidence base these outcomes are associated with considerable uncertainties.
- The Appraisal Panel encourages further research on the use of Synovasure® testing in the diagnosis of peri-prosthetic hip and knee joint infection. It considers that the greatest potential clinical value is in patients in whom standard clinical and laboratory testing has led to equivocal outcomes and it would therefore encourage studies that investigate the added value of using POC Synovasure® testing on clinical decision making at the time of surgery. These studies should include an assessment of patient-related clinical outcome measures and costs.

EVIDENCE SUMMARY

For a full report of the evidence supporting this Guidance, refer to Evidence Appraisal Report 008.

Context

PJI is difficult to diagnose since there are no definitive tests and the symptoms resemble those of other conditions (such as aseptic loosening). The diagnosis is based on clinical and laboratory testing criteria which were incorporated into recommendations from the Musculoskeletal Infection Society (MSIS). These diagnostic criteria were widely adopted after 2013 and have since been updated to reflect the advent of new biomarkers.

The management of PJI differs from other causes of arthroplasty failure and the accurate diagnosis is therefore essential to guide subsequent care and choice of treatment pathway. Missing a diagnosis of PJI can lead to delayed intervention and a more complex re-operation at a later date while incorrectly diagnosing PJI in a patient without infection could lead to unnecessary surgery.

The Synovasure® test identifies elevated levels of alpha defensin, in synovial fluid which is proposed as a biomarker for predicting PJI. The test is available in two formats (both with Class 1 CE marks):

1. a laboratory-based ELISA (enzyme-linked immunosorbent assay)
2. a lateral flow immunochromatographic point of care test.

Both tests are indicated for pre-operative use as an adjunct to existing diagnostic tests particularly when these are equivocal, or confounded by pre-existing conditions. The point of care test can also be used intra-operatively during a revision procedure to rapidly assist decision making.

The manufacturer is proposing a lab service which would provide the Synovasure® ELISA test alongside other tests specified in the MSIS 2018 protocol. In current clinical practice, the Synovasure® test is typically used in patients with equivocal results after standard tests.

Evidence on clinical effectiveness, safety, economic analysis and patient issues

A large amount of literature was identified on the diagnostic accuracy of the Synovasure® laboratory test and lateral flow point of care test when used alone. Evidence from two systematic reviews showed that the Synovasure® laboratory test and Synovasure® lateral flow point of care test have good diagnostic accuracy for detecting PJI. The Synovasure® laboratory test was shown to have pooled sensitivity and specificity values of 95% and 97%, respectively in both systematic reviews. The Synovasure® lateral flow point of care test was shown to have pooled sensitivity and specificity values of 77% and 91%, respectively in one systematic review and 85% and 90% in another systematic review. However, in clinical practice the Synovasure® test would be used in combination with other tests and therefore studies showing the diagnostic accuracy of Synovasure® when used alone are of somewhat limited interest.

One relevant study was identified which considered the use of Synovasure® in combination with other tests. This was a retrospective analysis of patients undergoing hip and knee revisions which was done to develop and externally validate new diagnostic criteria for PJI that incorporate the Synovasure® test. The external validation component was based on 222 infected and 200 aseptic revisions. The diagnostic accuracy of the new criteria was compared against older diagnostic criteria. The new criteria were found to have a sensitivity of 97.7% and a specificity of 99.5%. The older diagnostic criteria from 2013 was found to have a sensitivity of 86.9% and a specificity of 99.5%.

There is, however, the potential for bias since the sensitivity and specificity calculations reported for the new diagnostic criteria exclude patients with inconclusive results. Furthermore, while the evidence from this study provides the best available evidence on the use of Synovasure® in combination with other tests, it does not match the most recent diagnostic criteria.

One relevant study was identified which considered the use of the Synovasure® lateral flow point of care test in patients with equivocal results after standard testing. It was a single centre, prospective, non-randomized study in France that included 42 cases in 39 patients. The Synovasure® lateral flow point of care test was found to have a sensitivity of 88.9% and specificity of 90.6% in microbiologically complex situations that presented diagnostic challenges. The results demonstrate the potential utility of using the Synovasure® lateral flow point of care test in this group of patients but the small study population means that further evidence is needed to confirm the findings and also to explore clinical outcomes resulting from this decision making.

An economic model was developed to estimate the cost-effectiveness of the Synovasure® test in two scenarios:

1. using the Synovasure® laboratory test as part of a package of laboratory tests in all patients with suspected PJI
2. using the Synovasure® lateral flow point of care test in patients who had equivocal results with standard tests

The Synovasure® laboratory system was found to be more effective but more costly than standard testing in all modelled patient groups with an incremental cost-effectiveness ratio (ICER) above a threshold of £20,000 per QALY. Therefore the Synovasure® laboratory test was not deemed to be cost-effective in the base case analysis. The result was found to be insensitive to changes in most model inputs. However, the result was very sensitive to changes in relative diagnostic accuracy (particularly specificity). In probabilistic sensitivity analysis the lab system with Synovasure® was found to have a 0%, 2% and 0% probability of being cost-effective at a threshold of £20,000 per QALY in the hip, knee and overall population, respectively

The Synovasure® lateral flow point of care test was found to be more effective but more costly than standard testing in all modelled patient groups with an ICER below a threshold of £20,000 per QALY in knee revisions but above the threshold in hip revisions or in the overall population. The conclusion of the analysis was found to change in many scenarios modelled in sensitivity analysis with the result found to be sensitive to changes in diagnostic accuracy, PJI prevalence and QoL values. In probabilistic sensitivity analysis the Synovasure® lateral flow point of care test was found to have a 19%, 62% and 39% probability of being cost-effective at a threshold of £20,000 per QALY, in the hip, knee and overall population, respectively

The unit cost of the Synovasure® laboratory test when used with other standard tests was estimated to be £450. Based on 416 hip revisions and 324 knee revisions, the overall budget impact associated with using the laboratory service was estimated to be £229,555 for hip revisions and £136,363 for knee revisions with a combined impact of £365,918.

The unit cost of the Synovasure® lateral flow point of care test is £495 when purchased individually or £300 when purchased in a pack of 5. Based on 83 hip revisions and 65 knee revisions, the overall budget impact associated with the Synovasure® lateral flow point of care test was estimated to be £90,918 for hip revisions and £41,532 for knee revisions with a combined impact of £132,450.

Organisational issues

Currently there is no laboratory-based testing of alpha defensin available in the UK. The nearest approved laboratory is in Germany. Zimmer Biomet has plans to license the hospital laboratory

and provide a laboratory testing service in the UK. This testing service would provide alpha defensin alongside other tests specified in the MSIS 2018 protocol.

The alpha defensin point of care test has been employed in around fifteen different hospitals within Wales, although experts note limited use in those centres due to cost constraints. As detailed in the Welsh Government policy on the Management of Point of Care testing (Welsh Scientific Advisory Committee 2017), point of care diagnostic tests should be subject to scrutiny and quality control, including assessment in an appropriate external laboratory.

Further research

Further diagnostic studies are needed which compare the diagnostic accuracy of the laboratory based Synovasure® package of tests with standard practice and the use of Synovasure® in patients that have equivocal results after standard testing. These studies should include the gathering of patient related outcomes and costs so that the relative value of the different tests can be assessed in an economic evaluation

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality of care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTWs evidence review methods and framework for producing its guidance are available from the HTW website.

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Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTWs Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.


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