Innovative Medical Technology Overview: Number 009/2017

This IMTO summarises a submission by Zimmer Biomet regarding the following medical technology. It should be read in conjunction with the accompanying IMTO Review Document (RD), which is an impartial review of the strengths and weaknesses of the evidence submission by Healthcare Improvement Scotland.

Synovasure® alpha defensin lateral flow test kit

Technology

The Synovasure® alpha defensin lateral flow test kit is a point of care device designed to aid in the diagnosis of periprosthetic joint infection (PJI). The manufacturer does not currently recommend Synovasure® as a stand-alone test, but rather that it may be used along with other clinical and diagnostic assessments.

The Synovasure® alpha defensin lateral flow test kit comprises a single use device, similar in size and function to a home pregnancy test. It measures the levels of alpha defensin in the synovial fluid of people who have had a total joint replacement. A control line appears if the test has been performed correctly, and a second line appears if the level of alpha defensin in the sample is greater than a cut-off concentration (approximately 8µg/ml). Results are available in 10 minutes. The Synovasure® point of care test is CE marked as a class 1 device.

Accurate diagnosis of PJI is important, as the presence or absence of an infection guides the complexity of subsequent surgical management. Symptoms of PJI can be subtle in their presentation, particularly in delayed or late infections, and there is no single accepted set of diagnostic criteria for PJI.

Product Performance

Studies included within the review either: evaluated the point of care Synovasure® alpha defensin lateral flow test kit; or measured alpha defensin in the laboratory setting.

Laboratory-based immunoassay

Amongst the evidence presented by the manufacturer were two recent systematic reviews (with meta-analyses), encompassing seven studies in total. In all seven studies, alpha defensin was measured in the laboratory setting. One review from 2016 included six studies.

Economic considerations

The cost of the Synovasure® alpha defensin lateral flow test kit is £495 per test when purchased individually; and £300 per test when purchased in boxes of five.

The manufacturer presented a budget impact model to illustrate the potential impact on NHSScotland of using Synovasure® for the diagnosis of PJI prior to revision of total hip arthroplasty (THA) and total knee arthroplasty (TKA), as compared to the current standard of care (SoC). Individual models were presented.
(2,321 patients; 363 with an infection). The authors reported a pooled sensitivity and specificity for alpha defensin in diagnosing PJI of 1.00 (95% CI 0.82 to 1.00) and 0.96 (95% CI 0.89 to 0.99) respectively. The other review, from 2017, encompasses largely the same evidence base, and reports very similar results.

There is uncertainty surrounding the level of heterogeneity within the studies. One review highlighted a high level of heterogeneity as measured using the $I^2$ value, and the other did not report an $I^2$ value. That said, heterogeneity measured using the $I^2$ value may be difficult to interpret in diagnostic study meta-analyses; the context in which the test is used will often vary, as will the choice of thresholds used to define positive/negative results, leading to inevitable variation in sensitivity and specificity between studies.

Both reviews were appropriately cautious in their conclusions, noting the need for more research in the area.

*The Synovasure® point of care test*

Five published studies were identified that evaluated the point of care Synovasure® alpha defensin lateral flow test kit.

Two studies reported accuracy results that were comparable to the laboratory-based immunoassays. The first included 121 patients, and reported a sensitivity of 97.1% (95% CI 84.5 to 99.9), and a specificity of 96.6% (95% CI 90.3 to 99.2). The second included 51 patients (16 with infection as defined by MSIS criteria), and reported a sensitivity of 87.5% (95% CI 74.6 to 94.7) and a specificity of 97.1% (95% CI 86.9 to 99.7).

Conversely, in three small studies published in 2016 and 2017 (including 50 patients or fewer) which evaluated the point of care Synovasure® alpha defensin lateral flow test kit, the reported sensitivities were lower (69%, 67% and 76.9%). Specificities were 94%, 93% and 82.4%.

The manufacturer submission also included details from two conference abstracts, and a company paper, which all report high accuracy of the Synovasure® alpha defensin lateral flow test kit. However, the detail from these is insufficient to allow study appraisal.

from the perspective of the entire Scottish revision THA and TKA population and, additionally, from the perspective of the equivocal results population.

Overall, the budget impact model suggests that adding Synovasure® alongside SoC may result in net savings for NHSScotland. These savings are driven by the relatively higher accuracy of Synovasure® (0.97 sensitivity and 0.96 specificity) compared to current SoC (assumed sensitivity and specificity of 0.85 and 0.81 respectively) which reduces rates of false positives/negatives, thereby increasing the likelihood of optimising treatment allocations. However, it is not clear whether the high accuracy of Synovasure® assumed in the model is reflected in real world evidence and further sensitivity analysis has shown the net saving to be very sensitive to drops in test accuracy, specificity in particular. Threshold analysis indicates Synovasure® is not cost saving when specificity drops below 0.87 for the THA population and 0.84 for the TKA population, assuming all else is held equal.

Other limitations of the economic model are discussed in the review document.
Further testing and evaluation is encouraged to help clarify the uncertainty around the accuracy of the Synovasure® point of care test and determine its actual value in clinical practice.

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<th>Safety</th>
<th>Organisational and patient issues</th>
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<td>The manufacturers state that the test utilises fluid obtained during routine analysis, and does not require further invasive investigations. Therefore, they state that it does not introduce an additional safety risk to patients or staff.</td>
<td>Improved diagnosis of PJI may result in more efficient use of NHS resources.</td>
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<td>Point of care tests in NHSScotland are subject to scrutiny and quality control. This normally involves a small proportion of tests being repeated in the laboratory setting. Consideration needs to be given on what measures will be in place to ensure that the Synovasure® alpha defensin lateral flow tests are being used appropriately. Given the subjective nature of the test, it may be prone to errors in timing and visual interpretation. Therefore there is a need for adequate training to avoid errors in use.</td>
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<td>No information relating to patient issues was mentioned in the manufacturer’s submission; and none was identified from the literature search conducted by staff at Healthcare Improvement Scotland.</td>
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**What is an IMTO?**

Innovative Medical Technology Overviews (IMTOs) summarise the evidence relating to an individual technology that has been submitted by the manufacturer of the technology.

The purpose of IMTOs is to provide information that will contribute to local decision-making by NHS health professionals, NHS managers, and procurement colleagues.

IMTOs do not contain recommendations for NHSScotland and should be considered alongside existing guidance applicable to NHSScotland.

**Chair**

**Scottish Health Technologies Group**