Innovative Medical Technology Overview: Number 009/2015

This IMTO review document describes an impartial review of the strengths and weaknesses of the submission by Zimmer Biomet regarding the following medical technology.

Synovasure® Alpha Defensin Lateral Flow Test Kit

Overview of technology

The Synovasure® alpha defensin lateral flow test kit is CE marked as a class 1 device. It measures human alpha defensins 1-3 in the synovial fluid of people who have had a total joint replacement. Alpha defensins are antimicrobial peptides released by activated neutrophils in response to infection\(^1\). The Synovasure® test is intended to aid in the diagnosis of periprosthetic joint infection (PJI), along with other clinical and diagnostic assessments\(^2\).

The Synovasure® alpha defensin lateral flow test kit comprises a single use device, similar in size and function to a home pregnancy test. It is a point of care device, which can be used during pre-operative joint aspiration or intra-operatively during revision procedures. Small amounts of synovial fluid are collected with the Microsafe® tube and added to a premeasured dilution buffer. Three drops of this sample are then added to the test device. 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\(^2\).

In 2015, there were 7,907 hip replacements and 7,881 knee replacements in Scotland; and there were 830 revision hip and 470 revision knee procedures\(^3\). Figures from the United States suggest that PJI complicates around 1-2% of joint replacements\(^4\). PJI is the cause of 20-25% of total knee arthroplasty failures; and 12-15% of total hip arthroplasty failures\(^5\). It can lead to additional surgeries, revision, fusion, amputation and in rare cases death\(^6\).

An accurate diagnosis of PJI ensures appropriate treatment. The incorrect diagnosis of a PJI in a healthy patient (a false positive result) can lead to more complex surgical management than is actually required. Conversely, a false negative result can lead to less optimal treatment allocations, delayed intervention, and more complex re-operation at a later date. An early diagnosis can lead to less radical treatment\(^7\). The cost of a revision for infection has been estimated to be more than three times than that of an aseptic revision\(^8\).

Comparator(s) and use in pathway of care

The most common symptom of PJI is nonspecific pain. In patients presenting with nonspecific pain, tests are used to differentiate between septic and aseptic causes. This guides subsequent management.
PJIs is categorised based on the time since initial surgery. An early infection develops within 3 months of surgery; a delayed infection develops from 3 months to 2 years after surgery; and a late infection develops 2 years after surgery\(^4\).

In an acute infection, the signs of inflammation are generally present. These include pain, swelling, erythema and warmth. Delayed and late infections are often more subtle in their presentation, making diagnosis difficult\(^5\). Pain is commonly reported, as is loosening of the prosthesis. There is no single accepted set of diagnostic criteria for PJI\(^9\).

In 2013, the Musculoskeletal Infection Society (MSIS) convened a consensus group to propose a standard definition of PJI which could be universally adopted\(^10\):

1. A sinus tract communicating with the prosthesis.
   \[\text{Or}\]
2. Isolation of a pathogen from two or more periprosthetic cultures from the affected joint.
   \[\text{Or}\]
3. Three of the following:
   a. Elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
   b. Elevated synovial fluid white blood cell (WBC) count
   c. Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
   d. A single positive culture
   e. Positive histological analysis of periprosthetic tissue

The consensus group acknowledged that: an infection could still be present if these criteria were not met; and that some of these criteria may be met in the absence of an infection. The manufacturer’s submission also states that few hospitals have the resources to run all of the MSIS criteria tests.

Generally speaking, there is a need to confirm the presence or absence of infection when standard tests have failed to provide an accurate diagnosis.

The submission from Zimmer Biomet advises that the Synovasure® alpha defensin lateral flow test kit may be useful to aid the diagnosis of PJI at various stages in the patient pathway:

1) Pre-operatively: Synovasure® to be used as an adjunct to existing diagnostic tests.
2) Pre-operatively: when standard laboratory test results are equivocal and/or where the patient has a pre-existing condition that would chronically raise inflammatory markers and confound routine investigations.
3) Intra-operatively: Owing to the quick turnaround time for the results, where there are doubts upon commencement of the surgical procedure, the Synovasure® alpha defensin lateral flow test kit may be used during the operation to help determine whether the joint is infected or not. This will help to guide the required complexity of surgical revision.
Product performance

Published studies

The main evidence for this section comes from published studies included in the manufacturer’s submission: two systematic reviews (with meta-analyses)\(^7\),\(^1\) two prospective studies\(^2\),\(^1\) and one retrospective study\(^4\). In addition, a search conducted by staff at Healthcare Improvement Scotland yielded two more studies\(^5\),\(^6\). Finally, two studies were highlighted by the manufacturer, which were published after they made their initial submission\(^7\).

In most of the primary studies, alpha-defensin was measured in the laboratory setting, using immunoassays. The laboratory based testing utilises a Synovasure® test (from the same manufacturer), but not specifically the ‘alpha defensin lateral flow test kit’, which is described in the manufacturer’s submission as a point of care device. The laboratory-based tests require samples to be sent in to affiliated laboratories, with results normally made available to the clinician within 24 hours. The laboratory-based test is not available in NHSScotland. However, the studies assessing both the point-of-care tests and laboratory based tests have been included below, with the differences in accuracy results being discussed.

One of the systematic reviews (Wyatt \textit{et al}, 2016)\(^7\) synthesised the available evidence on the accuracy of alpha-defensin for the diagnosis of PJI. Six studies were included, encompassing 2,321 patients (363 with an infection). The studies all measured synovial fluid samples for alpha-defensin in the laboratory setting.

The authors stated that the reference standard in all included studies was the MSIS criteria (though this was not the case for the largest study included – see ‘strengths and limitations of the evidence’ section). Most of the patients had a hip or knee arthroplasty, but some had a shoulder arthroplasty. The authors stated that the included studies were of good quality. The pooled diagnostic sensitivity\(^*\) and specificity\(^†\) of alpha-defensin for PJI was 1.00 (95% CI 0.82 to 1.00) and 0.96 (95% CI 0.89 to 0.99). However, the \(I^2\) statistics for sensitivity and specificity were high (98.2% and 98.8%), indicating considerable heterogeneity between the studies. The area under the curve (AUC) for alpha-defensin and PJI was 0.99 (95% CI 0.98 to 1.00). The authors concluded that the diagnostic accuracy of alpha-defensin for the diagnosis of PJI was high, but that there was a need for more research to establish its clinical and cost effectiveness.

The other systematic review included in the manufacturer’s submission (Xie \textit{et al}, 2017)\(^1\) had a more limited literature search (PubMed only), but otherwise appears to be well conducted. The authors included six studies (five of which were included in Wyatt \textit{et al}, 2016). The pooled diagnostic accuracy results (sensitivity, specificity and AUC) were very similar to those reported by Wyatt \textit{et al}, 2016. Pooled sensitivity was 0.96 (95% CI 0.85 to 0.99), pooled specificity was 0.95 (95% CI 0.89 to 0.98), and pooled AUC was 0.99 (0.97 to 0.99). The \(I^2\) statistic was not reported for the pooled sensitivity and specificity, but the authors stated that there were ‘no signs of heterogeneity’. The overall conclusions mirror those made by Wyatt \textit{et al}.

\(^*\) Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, ie, the number of true positive results divided by the total number with the disease.

\(^†\) Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, ie, the number of true negative results divided by the total number of those without the disease.
alpha-defensin has a high diagnostic value for the detection of PJI, but that more large-scale and well-designed studies should be performed to confirm the optimal cut-off values.

The manufacturer’s submission highlighted three additional studies, which were not included in the above reviews:

- **Bonanzinga et al (2017)**
  This prospective study included 156 patients presenting with painful hip/knee arthroplasty. The aim was to determine the accuracy of the laboratory-based alpha-defensin immunoassay test in the diagnosis of PJI. A diagnosis of PJI was confirmed in 29 patients, using the MSIS criteria. In this study, the alpha-defensin test had a sensitivity of 97% (95% CI 92% to 99%), a specificity of 97% (95% CI 92% to 99%), a positive predictive value (PPV) of 88% (95% CI 81% to 92%), and a negative predictive value (NPV) of 99% (95% CI 96% to 99%). The authors concluded that the alpha-defensin assay appears to be a reliable test, but there is a need for longer-term follow-up.

- **Sigmund et al (2016)**
  This prospective study included 50 patients with a clinical indication for revision arthroplasty, and aimed to determine the accuracy of the point of care Synovasure® alpha-defensin lateral flow test in diagnosing PJI. Based on modified MSIS criteria, 13 cases were categorised as septic revisions, 36 as aseptic and one was inconclusive. The sensitivity for Synovasure® was 69% (95% CI 46 to 92), the specificity was 94% (95% CI 86 to 100) and the AUC was 0.82 (95% CI 0.68 to 0.95). The authors conclude that the Synovasure® alpha-defensin lateral flow test kit may be a useful adjunct in the diagnosis of PJI.

- **Shahi et al (2016)**
  This retrospective study (n=106) aimed to establish whether prior antibiotic administration was associated with decreased alpha-defensin levels; and also whether alpha-defensin (measured in the laboratory setting) is a better test for PJI than traditional tests (ESR, CRP, WBC, PMN% and fluid culture) when prior antibiotics have been given. The authors concluded that the alpha-defensin test maintains its concentration and sensitivity for PJI when there has been prior antibiotic administration. In addition, among patients on antibiotics, the alpha-defensin test was more sensitive in detecting PJI than the ESR, CRP, fluid PMN% and fluid culture.

A search of the literature was also conducted by staff at Healthcare Improvement Scotland. This yielded two additional studies. These had been identified by the manufacturer’s literature search, but excluded from their submission due to study limitations, in particular their small size. The first included 40 consecutive patients who underwent either revision total hip or total knee arthroplasties, and aimed to determine the diagnostic accuracy of the point of care Synovasure® alpha-defensin lateral flow test for the intraoperative diagnosis of PJI. Modified MSIS criteria for the diagnosis of PJI were used as the reference standard. The authors reported that the Synovasure® alpha-defensin lateral flow test had a sensitivity of 67% (95% CI 35% to 89%), specificity of 93% (95% CI 75% to 99%), a PPV of 80% (95% CI 44% to 96%) and a NPV of 87% (95% CI 68% to 96%). Receiver operator curve analysis demonstrated an AUC of 0.80.

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1 Positive predictive value: the probability that a person with a positive test is a true positive (ie has the disease).

2 Negative predictive value: the probability that a person with a negative test is a true negative (ie does not have the disease).
The second small single centre study included 28 consecutive patients (30 joints) with removal of total hip arthroplasty and total knee arthroplasty\(^\text{16}\). Patients were classified according to modified MSIS criteria. The authors reported that the point of care Synovasure\(^\circ\) alpha defensin lateral flow test had a sensitivity of 76.9\%, a specificity of 82.4\%, a NPV of 85\%, a PPV of 81\% and an accuracy of 0.83. The authors concluded that the alpha-defensin test was a good addition to the suite of tests available. However, compared to clinical classification, blood investigation and multiplex-PCR, the authors also noted that they could not find a clear advantage of using this test considering its costs and the yes/no information provided\(^\text{16}\).

Finally, the manufacturers highlighted two additional studies published after they made their initial submission. The first evaluated the diagnostic accuracy of the point of care Synovasure\(^\circ\) alpha defensin lateral flow test\(^\text{17}\). This prospective study included 121 patients (85 total knee arthroplasties and 36 total hip arthroplasties) with chronically painful prosthesis undergoing a joint aspiration in a diagnostic pathway, or during revision surgery. A modified version of the MSIS criteria was used as the reference standard, with the minor criteria ‘positive histological analysis of periprosthetic tissue’ being replaced with ‘purulence in the affected joint’. This change to the criteria was made as an experienced pathologist specialised in musculoskeletal diseases was not available during surgery in two out of the three participating centres for frozen section investigation. The authors concluded that the point of care Synovasure\(^\circ\) alpha defensin lateral flow test had a sensitivity of 97.1\% (95\% CI 84.5 to 99.9), a specificity of 96.6\% (95\% CI 90.3 to 99.2), a PPV of 91.7\% (95\% CI 77.7 to 98.3) and a NPV of 98.8\% (95\% CI 93.6 to 99.9). The AUC was 0.97 (95\% CI 0.93 to 1.00). In this study, the surgeon in charge was asked to use available clinical data to assess whether the prosthesis was infected and to clarify their intention-to-treat pre-operatively (i.e. before assessing biofilm and before the Synovasure\(^\circ\) test results were made available). The authors reported that the surgeons did not change their surgical plan when the result of the Synovasure\(^\circ\) test was revealed. The authors concluded that the test has ‘a promising diagnostic potential’ but that ‘given the high cost of this test at face value, further economic analysis is necessary to evaluate cost-effectiveness’.

The second study, submitted by the manufacturers after their initial submission, included 51 patients (16 with infection as defined by the MSIS criteria) who presented with failed or painful joint arthroplasty. The Synovasure\(^\circ\) alpha defensin lateral flow test was performed preoperatively, or during surgery. The MSIS criteria was used as the reference standard. The authors reported a sensitivity of 87.5\% (95\% CI 74.6 to 94.7), a specificity of 97.1\% (95\% CI 86.9 to 99.7), a PPV of 93.3\% (95\% CI 81.8 to 98.1), and a NPV of 94.4\% (95\% CI 83.2 to 98.6). The authors acknowledge that their ‘relatively small sample may overestimate that accuracy of the test, so further studies are needed to evaluate the performance of Synovasure\(^\circ\) and its role in the diagnosis of infected arthroplasty’\(^\text{18}\).

Overall, the existing evidence reports high accuracy for alpha-defensin in the diagnosis of PJI, but notes the need for more research. The point of care Synovasure\(^\circ\) alpha-defensin lateral flow test kit gives a rapid result, and so it has potential for use in the intra-operative setting, when a fast result is required. It may also be a useful addition to the current suite of diagnostic tests done pre-operatively; but more research is needed to establish where in the patient pathway it has most value.
Laboratory-based immunoassay versus point of care test: variation in results between the two approaches

In most of the primary studies, synovial fluid samples were tested for alpha-defensin in the laboratory setting using immunoassays. In three studies that used the Synovasure® alpha defensin lateral flow test, a point-of-care device, the accuracy was lower (reported sensitivities were 69%\textsuperscript{13}, 67%\textsuperscript{15}, and 76.9%\textsuperscript{16} and specificities were 94%, 93%, and 82.4%). The manufacturer excluded two of these studies due to their size\textsuperscript{15, 16}. They also note that in two studies, there was blood contamination of the samples that might have affected the results\textsuperscript{13, 15}. Kasparek et al suggested that ‘centrifugation of the samples in combination with laboratory immune assays might be more accurate than the Synovasure® PJI lateral flow test’\textsuperscript{15}.

Conversely, two other studies submitted by the manufacturer after their initial submission, reported accuracy results for the point-of-care Synovasure® alpha defensin lateral flow test to be comparable with the laboratory based tests. Berger et al state that they did not centrifuge the samples in their study, and suggested that their improved results be due to: exclusion of people with a spacer in situ (included in the other studies); testing of patients with an arthroplasty in locations other than the hip or knee; and the use of a different modification of the MSIS criteria. Furthermore, Berger et al stated: ‘we also postulate that in our three centres the alpha-defensin test was conducted by thoroughly trained medical staff in a standardised fashion\textsuperscript{17}. The other study, by Balato et al, note the potential of the Synovasure® alpha defensin lateral flow test, but acknowledge their studies limitations and the need for more research\textsuperscript{18}.

Laboratory-based immunoassay versus point of care test: emerging evidence

In their topic referral, the manufacturer submitted emerging evidence - two conference abstracts\textsuperscript{19, 20} and a Zimmer Biomet company paper (details taken from manufacturer submission, but reference not available) - which all suggest that the accuracy of the Synovasure® alpha defensin lateral flow test is similar to the laboratory based immunoassays. The two conference abstract studies include 24 and 36 patients, and both report sensitivities and specificities of 100%. The company paper that the manufacturers refer to in their submission includes the results of 365 Synovasure® lateral flow tests and report a sensitivity of 92.65% (95% CI 86.89 to 96.42) and a specificity of 99.56% (95% CI 97.59 to 99.99). However, the detail from these is insufficient to allow study appraisal.

In addition, shortly before publication of this IMTO, a peer reviewer forwarded on a paper they had presented at the British Orthopaedic Association Annual Congress (2017), detailing a study evaluating the Synovasure® alpha defensin lateral flow test\textsuperscript{21} in a Scottish centre. Only high level detail is provided, but the study included 26 patients, and the authors reported a 100% sensitivity and 95% specificity. The authors concluded that the test aids diagnosis in selected cases, when robust routine first line investigation results are equivocal and infection is still suspected.
Safety

The manufacturer states that the test uses fluid obtained during routine analysis, and does not require further invasive investigations. They state that it does not introduce an additional safety risk to patients or staff.

Strengths and limitations of the evidence

Both of the systematic reviews appear to be of good quality in that, for example, they appraised the quality of the included studies, and had two reviewers perform data extraction. Their conclusions are appropriately cautious, both noting the need for more research in the area. There is uncertainty surrounding the level of heterogeneity between the studies.

The meta-analysis by Wyatt et al (2016) highlights the significant heterogeneity between the studies, as measured using the $I^2$ statistic. However, heterogeneity measured using the $I^2$ value is difficult to interpret in diagnostic study meta-analyses as sensitivity and specificity are expected to vary between studies due to the situation the test is being used in and the threshold effect (caused by included studies using different thresholds for a positive diagnosis). The authors suggest that future studies should aim to assess differences in diagnostic accuracy relating to potential sources of heterogeneity, including arthroplasty site, time since index surgery and patient characteristics. They make no mention of the threshold effect.

Wyatt et al (2016) note that a number of the studies came from the same research group, and that the included studies made no mention of blinding.

Xie et al (2017) noted some limitations of their meta-analyses, for example the inclusion of people with inflammatory disease (potentially increasing false positives); and the use of different alpha-defensin cut-off values (thresholds) in the different studies. They also note that few studies had a long-term follow-up. This may mean that some false negatives were missed (in people who tested negative for infection, but who actually had a low grade infection that became apparent in subsequent months).

Of the primary studies included in the two reviews, four were prospective and two were retrospective. Most of them included relatively small numbers of patients (between 30 and 149), but one retrospective study (Deirmengian et al, 2015) was much larger than the rest (n=1,937). Therefore the pooled results will have been heavily influenced by this one study. For this reason, this study was obtained and reviewed.

The aim of Deirmengian et al (2015) was not to determine the accuracy of alpha-defensin, but to establish the breadth of organisms that can trigger a positive alpha-defensin result, and assess the magnitude of the alpha-defensin result in terms of various pathogen characteristics. It reviewed the results of 1,937 samples that had been processed in a laboratory for alpha-defensin testing and a synovial fluid culture. The systematic reviews appear to have used the results from the synovial fluid culture as the reference standard to calculate sensitivity and specificity. A full clinical data set was not available for every synovial
fluid sample, preventing the assessment of the MSIS definition for PJI, and this is a shortcoming of the study.

As previously noted, there is no single accepted set of diagnostic criteria for PJI, and the MSIS consensus group acknowledge that their standard definition for PJI is not perfect. Most of the studies reviewed here stated that they used the MSIS criteria as a reference standard, or a modified version of the MSIS criteria. It is also worth noting that hospitals may not have access to the full suite of tests within the MSIS criteria.

**Economic considerations**

The cost of the lateral flow kit is £495 per test when purchased individually; and £300 per test when purchased in boxes of five. This is more expensive than some other tests on the MSIS criteria (for example, the leukocyte esterase colorimetric strip test is £0.11 per test)\(^7\).

The manufacturer presented a budget impact model to illustrate the potential effect of incorporating the use of Synovasure® during the diagnosis of PJI prior to revision total hip arthroplasty (THA) and total knee arthroplasty (TKA) procedures, as compared with the current standard of care (SoC).

The model is built on the premise that Synovasure® offers a higher sensitivity and higher specificity than the current suite of diagnostic tests. As previously described, an accurate diagnosis of PJI ensures appropriate treatment. The incorrect diagnosis of a PJI in a healthy patient (a false positive result) can lead to more complex surgical management than is actually required. Conversely, a false negative result can lead to less optimal treatment allocations, delayed intervention, and more complex re-operation at a later date.

Two budget models were presented; one based on the introduction of Synovasure® alongside the existing suite of tests (i.e. the perspective of the entire Scottish revision THA and TKA populations), and a second based upon the use of Synovasure® only when other test results were equivocal.

**Model 1: Synovasure® as an adjunct to existing tests**

The model takes the PJI incidence rates of the revised THA and TKA populations and applies them to the actual number of Scottish THA and TKA revisions respectively, thus estimating the population of actual PJI and non-PJI cases.

The overall costs associated to the populations of PJI and non-PJI cases is estimated by applying the expected cost per PJI and non-PJI case respectively to the actual population numbers.

The expected cost in both cases is a function of the sensitivity and specificity of the diagnostic test(s) being used, as well as the costs of the subsequent interventions informed by the diagnosis. The subsequent interventions are classified as in Table 1.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Target population</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>THA revision</strong></td>
</tr>
<tr>
<td>1-stage revision</td>
<td>Patients with negative PJI diagnosis</td>
<td>£11,897</td>
</tr>
</tbody>
</table>
The manufacturer presented a number of cost estimates for surgical procedures which also included the NHS reimbursement tariff on top of the above costs. However, these were felt to be an overestimate of the true cost to the NHS and therefore, the costs in the economic model were changed to reflect the estimates for each procedure noted above.

Hence the expected costs are calculated in the following way:

$$E[\text{cost PJI patient}] = \text{sensitivity} \times (\text{cost 2 stage}) + (1 - \text{sensitivity}) \times (\text{cost 3 stage})$$

$$E[\text{cost non PJI patient}] = \text{specificity} \times (\text{cost 1 stage}) + (1 - \text{specificity}) \times (\text{cost 2 stage})$$

The model assumes that patients with a positive diagnosis receive a 2-stage revision, while cases with a negative diagnosis receive a 1-stage revision. However, given that the test may incorrectly attribute a negative diagnosis given that an infection is present, the patient is assumed to receive a 1-stage revision initially, followed by a deferred 2-stage revision (what is described in the model as a 3-stage revision) in such cases.

The model then calculates the expected costs per PJI and non-PJI patient in both the revision THA and TKA populations. These expected costs are applied to the actual number of PJI and non-PJI cases to get the overall costs for PJI and non-PJI cases in both populations. Test costs are also added to get the total cost associated to the THA and TKA populations.

Total costs are calculated under two scenarios: using the current SoC and using Synovasure® in addition to SoC. The difference in total costs is driven by the relative accuracy (sensitivity and specificity) and cost of using Synovasure® as compared with the SoC. The budget impact model estimates the difference between the total costs in the two scenarios, resulting in the net savings for NHSScotland presented in Table 1 below.

The key assumption in the model is that the use of Synovasure® alongside SoC in the diagnosis of PJI leads to a sensitivity of 0.97 and a specificity of 0.96. This is compared to SoC alone for which the sensitivity and specificity, 0.85 and 0.81 respectively, were calculated by taking a simple average of the sensitivity and specificity of the following four tests: ESR PJI, Serum CRP PJI, Synovial Fluid Cultures PJI, and Synovial Fluid WBC Count PJI.

The approach used for calculating the pooled sensitivity and specificity for the SoC appears overly simplistic and may not be representative of the clinical practice. The timing of the tests is crucial when the average accuracy of a battery or sequence of tests is evaluated in the

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
<th>Cost 1-stage (SoC)</th>
<th>Cost 3-stage (SoC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-stage revision</td>
<td>Patients diagnosed with PJI</td>
<td>£21,937</td>
<td>£30,011</td>
</tr>
<tr>
<td>3-stage revision</td>
<td>Described as a deferred 2-stage revision and given to false negative cases i.e. PJI cases with a negative diagnosis</td>
<td>£33,834</td>
<td>£39,666</td>
</tr>
</tbody>
</table>

* cost represents sum of costs for 1-stage and 2-stage revisions
* Vanhegan et al. 23
* Kallala et al. 8
clinical practice. If the tests are all being done at the same time regardless of the results from each other tests, then the tests should be evaluated as a clinical prediction rule. If they are being carried sequentially - with the results of one test determining whether the next test is carried out - then they should be evaluated in this sequence. The population will then need to be filtered at each testing stage to those who test positive at the previous step, and the correlation between the results needs to be incorporated. That said, generally speaking, it may be reasonable to assume that Synovasure® does indeed offer increased accuracy over the existing battery of tests.

Table 1: Budget impact of Synovasure® vs SoC in Scottish THA and TKA populations

<table>
<thead>
<tr>
<th></th>
<th>THA Population (n=830; PJI incidence = 13%)</th>
<th>TKA Population (n=470; PJI incidence = 23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SoC</td>
<td>SoC + Synovasure</td>
</tr>
<tr>
<td>PJI population revision cost</td>
<td>£2,559,555</td>
<td>£2,405,513</td>
</tr>
<tr>
<td>Non-PJI population revision cost</td>
<td>£9,968,302</td>
<td>£8,880,819</td>
</tr>
<tr>
<td>Population test cost</td>
<td>£820,040</td>
<td>£1,230,890</td>
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<tr>
<td>Total cost</td>
<td>£13,347,897</td>
<td>£12,517,222</td>
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<tr>
<td>Budget impact of Synovasure® (negative values represent net savings)</td>
<td>-£830,675</td>
<td>-£997,620</td>
</tr>
</tbody>
</table>

The results show that the increased test cost associated with Synovasure® is offset by a reduction in the cost of unnecessary or delayed surgical revision.

A key potential weakness in the analysis – based on the product performance evidence presented previously – is the uncertainty surrounding the relative sensitivity and specificity of the Synovasure® POC test. In order to test the impact of this uncertainty, the model was altered in order to determine how the budget impact would change if the sensitivity and specificity of the Synovasure® + SoC package was lower than 0.97 and 0.96 respectively.

Two-way sensitivity analysis below (Table 2 and 3) shows how variable the budget impact results are to the performance of Synovasure®.

Table 2: Net savings (£) of Synovasure® vs SoC in the THA population for different performance levels of Synovasure®

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>0.7</th>
<th>0.75</th>
<th>0.8</th>
<th>0.85</th>
<th>0.9</th>
<th>0.96</th>
</tr>
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<tr>
<td>0.69</td>
<td></td>
<td>1413727</td>
<td>1051233</td>
<td>688739</td>
<td>326244</td>
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<td>-471243</td>
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<td>0.75</td>
<td></td>
<td>1336706</td>
<td>974212</td>
<td>611717</td>
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<td>-548264</td>
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<td>910027</td>
<td>547533</td>
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<tr>
<td>0.85</td>
<td></td>
<td>1208337</td>
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<td>-241640</td>
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<td>1079969</td>
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Table 3: Net savings (£) of Synovasure® vs SoC in the TKA population for different performance levels of Synovasure®

<table>
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<th>Sensitivity</th>
<th>Specificity</th>
<th>0.7</th>
<th>0.75</th>
<th>0.8</th>
<th>0.85</th>
<th>0.9</th>
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The net savings following the introduction of Synovasure® seem to be more responsive to drops in specificity rather than sensitivity. According to the model provided by the manufacturer, the threshold at which the net saving for the THA population associated to Synovasure® + SoC versus SoC alone becomes zero is given by a specificity of 0.87 (assuming that the sensitivity of Synovasure® + SoC is the same as SoC alone [0.85]). For the TKA population, this specificity threshold is 0.84.

What this result means in practical terms is that Synovasure® + SoC would need to correctly identify at least six extra true negative cases per 100 non-PJI THA patients compared to the current SoC in order to result in net savings for the budget of NHSScotland. However, if the specificity of Synovasure® + SoC is not higher than for the SoC alone, Synovasure® will not result in any net savings for the THA population regardless of its sensitivity. For the TKA population, an extra three patients per 100 non-PJI would need to be correctly identified as true negative cases for the test to be cost saving.

It is also worth considering that the potential of Synovasure® to increase the accuracy of the current SoC can yield other benefits which have not been factored in the net savings estimated by the present budget impact model. For example, reducing the misidentification of PJI cases can potentially free up important healthcare resources (e.g. Scottish Orthopaedic Theatre time, Scottish general ward bed days) and their associated opportunity cost. Also, the impact on health utility scores of receiving the appropriate treatment in a timely fashion has not been taken into account.

**Model 2: Synovasure® use where existing tests equivocal**

The model assumes that 6% of the THA (n=50) and TKA (n=28) populations respectively yield equivocal results. This rate seems like a conservative and reasonable estimate and is based on hospital episode statistics data.

Each patient in the equivocal population tested with SoC will be diagnosed as PJI. Hence, within the arm without Synovasure® a 2-stage revision is applied to all equivocal cases in both THA and TKA populations.
Within the arm with Synovasure®, it is assumed that 8.3% of the equivocal population are actually PJI and 91.7% are non-PJI (manufacturers state that these figures come from the White et al. study\textsuperscript{20}, but figures could not be verified). Of the non-PJI 65% were treated with 1-stage revision and 35% were not treated. The model seems to assume that Synovasure® identifies correctly the diagnosis of all equivocal cases i.e. 100% accuracy. This high accuracy resulted in the White et al. study\textsuperscript{20}, but it is based on a small sample: 12 THA (5 aspirations and 7 intra-operative cases) and 24 TKA (17 aspirations and 7 intra-operative cases).

Based on the above assumptions, the use of Synovasure® results in net savings of £747,595 in the THA population and £656,621 in the TKA population. However, it should be noted that these results are based on the premise that the accuracy of Synovasure® is similar to that of laboratory based immunoassays as indicated in a conference abstract (White et al. paper; full study unpublished) submitted by the manufacturer as emerging evidence. This study has a small sample upon which it is difficult to draw any firm conclusions. The net savings are unlikely to be sustainable for a lower accuracy of Synovasure®.

**Organisational and patient issues**

More accurate diagnosis of PJI may result in more efficient use of NHS resources. False positives can result in patients receiving more complex surgical management than is required, at a greatly increased cost. False negatives can lead to less than optimal treatment allocations, with any revisions likely to fail, and the need for further interventions at a later date.

A retrospective study detailed above\textsuperscript{14} suggests that pre-existing antibiotic treatment does not influence Synovasure® test results, meaning that there is no requirement for patients to stop pre-existing antibiotic treatment.

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. Currently, there is no laboratory-based testing of alpha-defensin available in the UK. The nearest laboratory would be in Germany. Consideration needs to be given on what measures would 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.

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.

**Summary**

The Synovasure® alpha defensin lateral flow test is a point-of-care device, designed to aid in the diagnosis of preoperative or intraoperative PJI. It is not currently recommended by the manufacturer as a stand-alone test to diagnosis PJI.

Most of the evidence comes from two systematic reviews (with meta-analyses), which both reported high accuracy for alpha defensin in the diagnosis of PJI, but also note the need for more research. These were based on laboratory studies rather than the point of care Synovasure® alpha defensin lateral flow test. In three small studies which evaluated the point of care test in diagnosing PJI, the reported sensitivity was lower than the laboratory-based
studies. The manufacturer has provided emerging evidence, and two larger recently published studies, which suggest that the accuracy of the point of care Synovasure® alpha defensin lateral flow test and the laboratory based immunoassays is comparable.

The relative accuracy of the point of care test is important owing to the fact it underpins the manufacturer’s economic argument. Compared with usual care, if the addition of Synovasure® to the existing suite of tests increases the specificity surrounding PJI diagnosis, then it may lead to resource savings for the NHS.

This review shows some promising preliminary results. 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.
References