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THE BUDGET IMPACT OF THE SYNOVASURE® ALPHA DEFENSIN LATERAL FLOW TEST

PERIPROSTHETIC JOINT INFECTION (PJI)

Total joint arthroplasty is considered one of the most successful surgical interventions in the history of medicine. Infection around these implants, however, remains one of the biggest challenges facing orthopedics today. Periprosthetic Joint Infection (PJI) can lead to additional surgeries, revision, fusion, amputation and possibly even death.[1,2] In fact, one study by Gutowski ***et al*** reported that the five-year mortality rate for patients with PJI has been reported to be as high as 87%, comparable to a number of common cancers (Figure 1).[3]

The aging population, pre-existing comorbidities such as diabetes and obesity, and an increasing antimicrobial resistance has led to a surge in generalized musculoskeletal infection, including PJI.[3] Despite significant technological advancements in implants and techniques, PJI now accounts for 25% and 15% of failed total knee arthroplasties (TKA)[4] and total hip arthroplasties (THA),[5] respectively. Kurtz *et al* reported that upon data extrapolation over 60% of all revision total joint procedures will be due to PJI by 2030.[6]

The rise in incidence rate of PJI comes with severe economic burden to the overall health care system. **When compared to primary surgery, revision surgery in the setting of PJI is estimated to have an immense increase in cost, longer hospital stay, and a higher likelihood of readmissions.**[7] The gold standard for PJI revision involves a two-stage procedure in which the patient undergoes a surgical debridement of infected tissue, implant removal, and placement of an antibiotic spacer, and reimplantation after extended antibiotic treatment, often at least six weeks after the first stage. The cost of a two-stage treatment plan is estimated to be double the cost of a one-stage aseptic revision.[7] As such, a correct diagnosis of the cause of primary implant failure is imperative in the development of an effective and cost-efficient treatment plan.

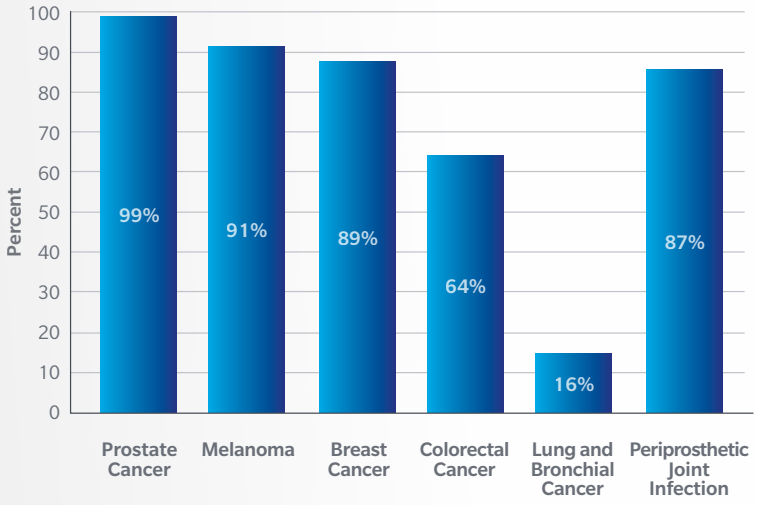


Figure 1: The five-year mortality rate for patients with PJI has been reported to be as high as 87%, comparable to a number of common cancers.[3]

Current Standard of Care for Diagnosing PJI

Unfortunately, the diagnosis of PJI is challenging. Acute infections may present similarly to inflammatory symptoms, while chronic PJI can be subtle and easily misdiagnosed. Although there is no single set of accepted criteria, the Musculoskeletal Infection Society (MSIS) published a consensus statement in 2013 aiming to provide a unified definition of PJI after hip and knee arthroplasty, which is summarized in Table 1.

Major Criteria			Decision
Two positive periprosthetic cultures of identical organisms			Infected
A sinus tract communicating with the joint			
Minor Criteria	**Threshold**		**Decision**
	Acute	Chronic	PJI is present if at least 3 out of 5 minor criteria exist
Elevated Serum ESR (mm/hr) and Serum CRP (mg/L)	N/A 100	30 10	
Elevated Synovial WBC (cells/µL) or Leukocyte Esterase	10,000 + or ++	3,000 + or ++	
Elevated Synovial PMN (%)	90	80	
Positive Histological Analysis of Periprosthetic Tissue	> 5 neutrophils per high power fields (x400)	> 5 neutrophils per high power fields (x400)	
Single Positive Culture			

Table 1: 2013 MSIS Criteria in the diagnosis of PJI[8]

Many of these standard of care (SoC) tests are affected by inflammatory conditions, limited technology, non-standardized cutoffs, and/or concurrent antibiotic treatment, which is reflected in the variable diagnostic accuracy seen in Table 2.

Standard of Care Tests[9]

	Sensitivity (true positive rate)	Specificity (true negative rate)
Serum Erythrocyte Sedimentation Rate (ESR)	86% - 94.7%	62% - 72.3%
Serum C-Reactive Protein (CRP)	82% - 96.6%	68.1% - 88%
Synovial Fluid WBC Count	85.7% - 89.5%	83% - 93%
Synovial PMN Percentage	85.8% - 92.1%	80.8% - 88%
Synovial Fluid Culture	62% - 73.8%	92% - 95.6%
Histological Analysis (Frozen Section)	74% - 86%	93% - 99%

Table 2: Sensitivities and specificities of the current standard of care in PJI diagnosis

Standardized preoperative workups are available as general guidelines in primary arthroplasty, but time constraints and patient variability in revision surgery may make it difficult to optimize the preoperative process.[10] Due to the variation in treatment in the presence of PJI and its unfavorable outcome when not properly addressed, one study recommends that every patient presenting with pain after joint replacement be considered infected until PJI can be effectively ruled out.[11] The initial history and physical examination play crucial roles in this process, but further testing is required to yield a confident diagnosis.

The SoC tests often utilized in US institutions as initial preoperative screening tools include serum ESR and serum CRP testing, although serum CRP has gained more popularity and trust among professionals in recent years. Negative CRP results are used to rule out infection, while positive results trigger joint aspiration to further test for the presence and type of infecting organism. In a recent large-scale systematic review, however, serum CRP displayed an average sensitivity and specificity of 84.5% and 81.3%, respectively,[12] leaving room for false negative diagnoses and missed infections.[12]

As a result of imperfect screening tests, intraoperative tests have gained popularity as measures to provide additional information on the presence or absence of infection. These are especially crucial in CRP negative cases where no further testing was performed. Currently, the AAOS recommends frozen section histological analysis in revision THA and TKA but also recognizes its shortcomings.[13] Although its relatively quick turnaround time lends itself to intraoperative use, the utility of frozen section remains controversial due to variation in clinical values noted in the literature and high dependence on the availability of experienced pathologists.[11] As the diagnosis of PJI dictates the type of treatment plan, false positive and false negative results from SoC tests can severely increase patient morbidity and an institution's economic burden. The use of an intraoperative test to aid in diagnosis of infection could reduce PJI associated costs.

Synovasure® Alpha Defensin Lateral Flow Technology

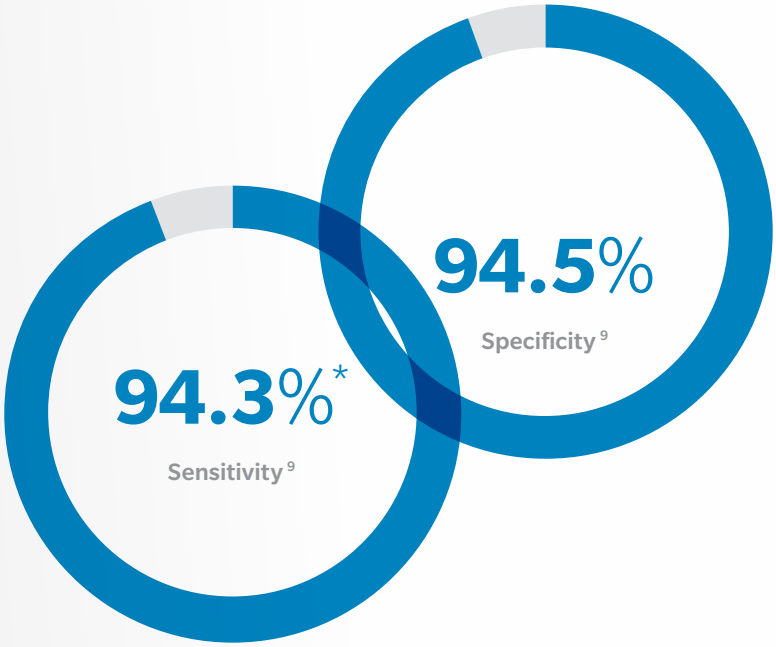
CD Diagnostics (a division of Zimmer Biomet) has validated the antimicrobial peptide alpha defensin as a significant biomarker in the detection of PJI[14] that is unaffected by concurrent antibiotic treatment or comorbid inflammatory conditions. The Synovasure Alpha Defensin ELISA (enzyme-linked immunosorbent assay) Test was launched in 2013 as a laboratory service to support the diagnosis of PJI with a 24-hour turnaround time.

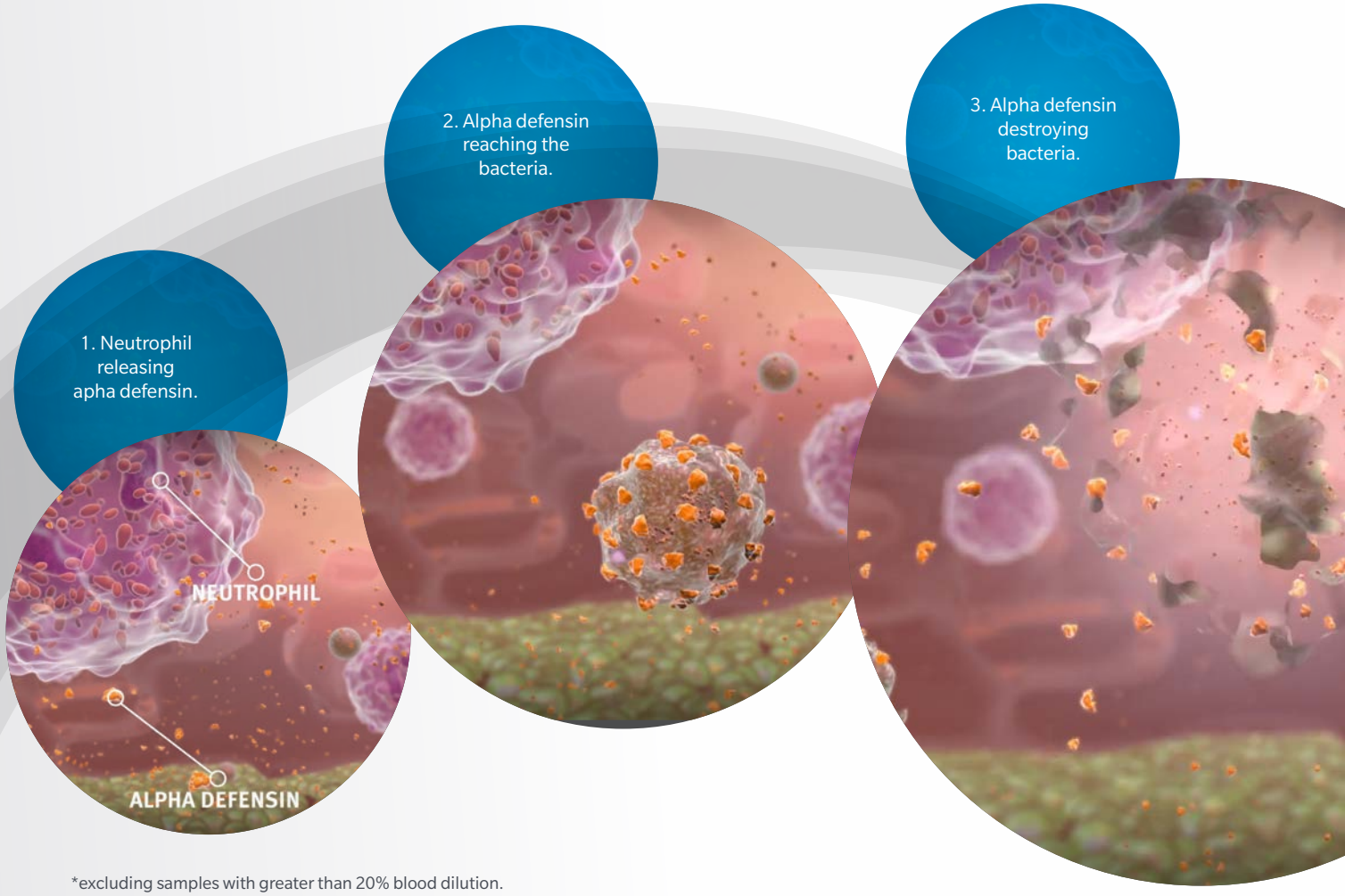
The Synovasure Alpha Defensin Lateral Flow Test is a rapid, highly sensitive and specific test which can provide results in ten minutes, making its use as an intraoperative confirmatory test for infection advantageous in the orthopedic community (Figure 2).[15]

Figure 2: Synovasure Alpha Defensin Lateral Flow Test.

In a recent comprehensive clinical study, the Synovasure Alpha Defensin Lateral Flow Test showed no statistically significant difference in performance compared to the Synovasure Alpha Defensin ELISA laboratory test,[16] with a reported sensitivity and specificity of 94.3% and 94.5%, respectively, excluding samples diluted more than 20% with blood.

When compared to SoC tests, the increased diagnostic accuracy realized by the addition of the Synovasure Alpha Defensin Lateral Flow Test reduces the economic burden of PJI by limiting misdiagnoses and unnecessary procedures. Its addition as an intraoperative confirmatory adjunct to a CRP work-up may reduce false negative diagnoses. In this scenario, a missed PJI infection could result in an unneeded aseptic one-stage revision followed by a septic two-stage revision, yielding a costly "three-stage" procedure to account for the missed infection. In eliminating false negative results, the device may save hospitals avoidable revision costs by giving physicians the tools to implement an optimum treatment plan.





*excluding samples with greater than 20% blood dilution.

Economic Model

A budget impact model was created to demonstrate the financial implications of improved diagnostic accuracy when using the Synovasure Alpha Defensin Lateral Flow Test in conjunction with serum CRP vs using serum CRP alone. These tests will report a certain number of negative and positive diagnoses, each consisting of true and false results according to its diagnostic accuracy. By using reported sensitivities and specificities of each test, a comparison in the amount of misdiagnosed cases can be provided. For this model it is assumed the true prevalence of infection for revision joint arthroplasty is 25% for revision TKA[4] and 15% for revision THA.[17] The equations for each outcome are listed below.

True Positive = (# revisions)*(PJI Prevalence Rate)*(Test Sensitivity)

True Negative = (# revisions)*(1-PJI Prevalence Rate)*(Test Specificity)

False Positive = (# revisions)*(1-PJI Prevalence Rate)*(1-Test Specificity)

False Negative = (# revisions)*(PJI Prevalence Rate)*(1-Test Sensitivity)

The Synovasure Alpha Defensin Lateral Flow Test is applied for every case screened as negative by serum CRP to model its utility as an intraoperative adjunct to this population. It is assumed that CRP positive results are flagged for further comprehensive synovial fluid testing and are not targeted in this model. Additionally, as the Synovasure Alpha Defensin Lateral Flow Test is to be used as an adjunctive test, all results should be considered in the context of other SoC results. Therefore, a discordant positive Synovasure Alpha Defensin Lateral Flow Test result in a CRP negative population is assumed to be flagged for further testing, such as intraoperative frozen section tissue analysis, to reduce false positive diagnoses. As a result, true and false positives provided by the device are not reported in the model and is instead centered on reducing the false negative diagnoses. The outline of the model is represented in Figure 3.

The model calculates approximated savings based on differences in one-stage and three-stage revisions, which are determined by the number of serum CRP negative cases correctly or incorrectly diagnosed in each scenario. Table 3 reflects the revision plan required by each diagnosis and median facility payment from commercial payers in the United States.

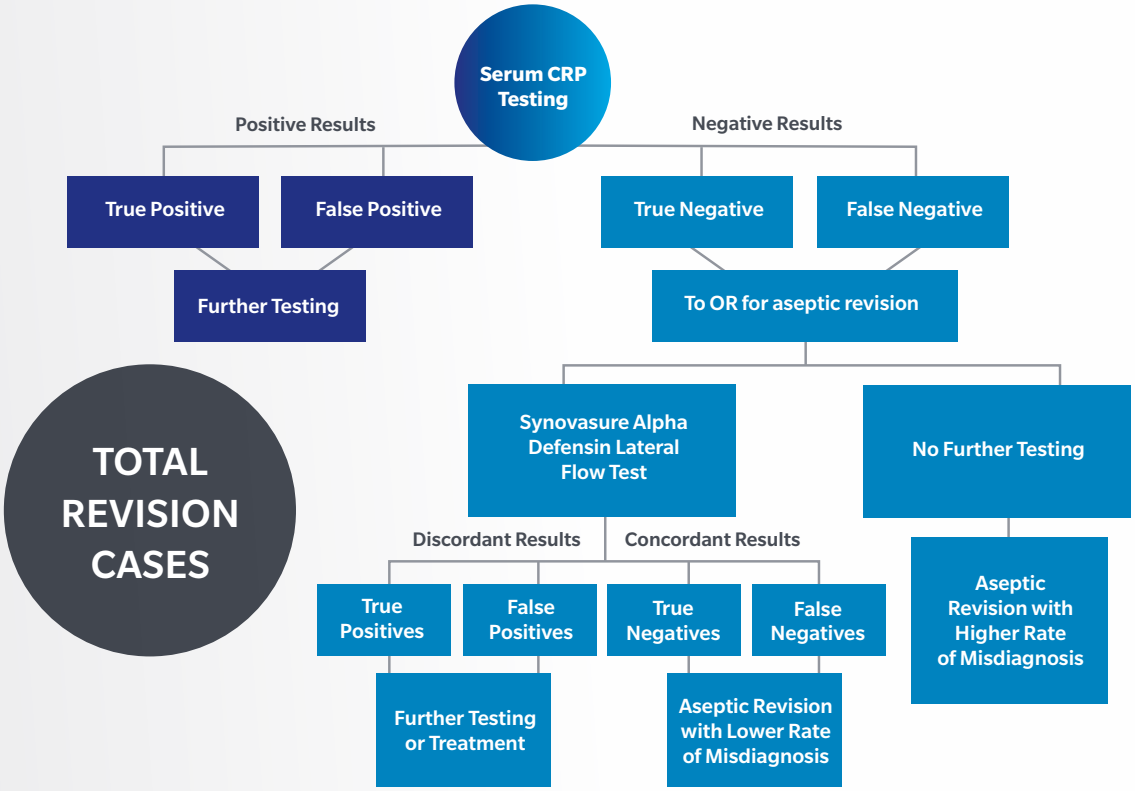


Figure 3: Flow chart of the clinical pathway assumed by the model to show potential cost savings when utilizing Synovasure Alpha Defensin Lateral Flow Test intraoperatively as an adjunct to standard of care screening tests.

Revision Plan	Target Population	TKA Cost[18]	THA Cost[18]
One-Stage Revision	True Negative Results	$40,062.45	$27,344.00
Two-Stage Revision*	True Positive and False Positive Results	$47,280.20	$46,726.90
Three-Stage Revision (One-Stage + Two-Stage)	False Negative Results	$87,342.65	$74,070.90

Table 3: Assumed treatment plan given to each diagnostic outcome with associated costs for hip and knee revision

*Positive results (true or false) are assumed to be flagged for further comprehensive synovial fluid testing and are not considered in this model.

Unnecessary revision costs are then calculated as follows:

Unnecessary Revision Costs=(Cost of 3 Stage-Cost of 2 Stage)*(# False Negatives)

For simplicity, the model assumes each revision plan to have success rates of 100%.

Case Study: Economic Impact Results for a Mid-Volume Institution

Potential savings offered when utilizing the Synovasure Alpha Defensin Lateral Flow Test in conjunction with Serum CRP is represented in the example of a mid-level volume institution, assuming a caseload of 300 revision knee and 120 revision hip arthroplasties per year.

Inputs:

Parameter Inputs	Serum CRP		Serum CRP + Synovasure Alpha Defensin Lateral Flow Test	
Type of Joint Revision Arthroplasty	**TKA**	**THA**	**TKA**	**THA**
Number of cases	300	120	300	120
PJI Incidence Rate in TKA Population (%)	25.2	15.0	25.2	15.0
Sensitivity, Specificity (%)*	84.5, 81.3		94.3, 94.5	
Test Cost (USD/case)**	0		450	

Table 4: Parameter input values for each scenario identified in the model

*Serum CRP values are based on an average of reported sensitivities/specificities. Serum CRP + Synovasure Alpha Defensin Lateral Flow Test values reflect clinical sensitivity/specificity of the Synovasure Alpha Defensin Lateral Flow Test alone.
**Serum CRP test costs are assumed to be reimbursed.

Cost of Missed Infections in TKA and THA Revision Cases				
		TKA Revision	THA Revision	**Total**
Serum CRP	**Negative Screens (True Neg + False Neg)**	193	85	**278**
	Missed Infections (False Neg)	13	3	**16**
	Unnecessary Revision Costs	$520,812	$82,032	**$602,844**
+ Synovasure Alpha Defensin Lateral Flow Test	**Missed Infections (False Neg)**	1	0	**1**
	Unnecessary Revision Costs	$40,062	$0	**$40,062**
		Reduction in Unnecessary Costs		**$562,781**
		Added Cost of Synovasure Alpha Defensin Lateral Flow Test		**$125,100**
		Total Savings		**$437,681**

Table 5: Output values produced by the model using parameter inputs in Table 3

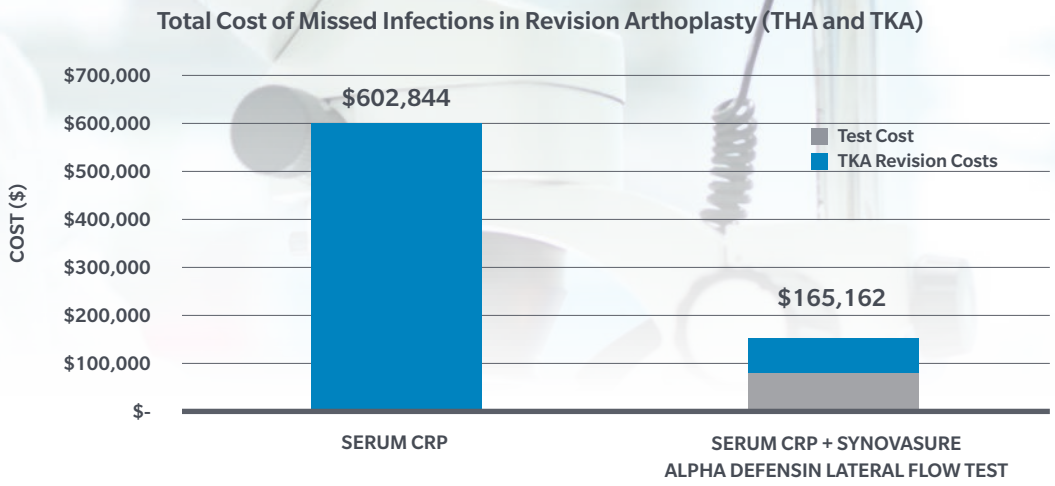


Figure 4: Model outputs in comparison of 420 total revision cases (300 TKA and 120 THA) diagnosed by serum CRP alone vs in conjunction with the Synovasure Alpha Defensin Lateral Flow Tests

15

Missed PJI diagnoses identified

$1,042

saved per revision patient

437,681

saved in unnecessary revision costs

Discussion and Other Considerations

With a decrease in PJI misdiagnosis, the budget impact model predicts a significant reduction in economic burden. Still, in assuming that all Serum CRP negative results are deemed absent of infection, the model could be viewed as simplistic. It does not account for the traditions of some physicians to obtain further test results in all scenarios and ignores the possibility of a case's unique presentation that could be indicative of infection. However, these assumptions are considered routine at most institutions, which adds to the model's credibility.

The model also omits a reduction in savings due to additional false positive diagnoses when the Synovasure Alpha Defensin Lateral Flow Test is used intraoperatively. These cases are assumed to be flagged for further testing and should therefore display low rates of misdiagnosis in the presence of a full work-up. As missed infections may facilitate devastating three-stage revisions, false negatives are prioritized in the model. However, the high sensitivity of the Synovasure Alpha Defensin Lateral Flow Test still limits the extent of false positive diagnoses.

Furthermore, the model's assumptions may underestimate the extent of predicted savings associated with the use of Synovasure Alpha Defensin Lateral Flow Test. The model assumes 100% success rate with all procedures, but with reported rates as low as 87% for THA and 72% for TKA revision procedures,[19] the vitality of a correct diagnosis is furthered. Additionally, cost data of joint revision is highly heterogenous, and wide disparities among US institutions have been reported.[20] Revision costs will vary based on institution and patient-specific parameters, but this model provides a conservative estimate. The assumption that a costly three-stage revision procedure driven by false negatives is the simple sum of a one and two-stage revision may be an underestimation. As antibiotic resistance continues to become problematic, the cost for PJI treatment has been estimated at $60,000 - $100,000, depending on the sensitivity of the pathogen and the treatment undertaken.[21]

Lab personnel time

Rapid results

Minimal Impact to OR time

The model focuses on reporting reductions in economic burden and therefore fails to reveal additional utilities of the Synovasure Alpha Defensin Lateral Flow Test. As a test that is rapid and easily performed, lab personnel time and duration of the surgical event after incision may be reduced. Time with open incision in the Operating Room (OR) has been shown as a significant risk factor for PJI and is reported to increase 25% for every additional 20 minutes,[22] with an associated cost increase estimated to be $34.00 per minute.[23] Frozen section histological analysis, a common intraoperative tool, exhibits average turnaround times over twenty minutes in the presence of a skilled pathologist and requires an open incision to be performed.[24] The Synovasure Alpha Defensin Lateral Flow Test device, on the other hand, requires aspiration before incision. Reducing OR time after incision could provide additional savings while reducing the risk of further infection when waiting for feedback from pathology.

With high utility as an adjunctive test for confirming PJI diagnosis intraoperatively, the model is focused on the population labeled as negative for infection by serum CRP. However, the Synovasure Alpha Defensin Lateral Flow Test could prove beneficial for patients, including those with serum CRP positive results. No test or combination of tests displays 100% sensitivity and specificity, and additional clarification on the presence or absence of PJI can improve confidence in the planned modalities, reduce unnecessary surgeries, and decrease burden on patient health. The two-stage revisions used to treat PJI are associated with a higher mortality rate, reported in literature to reach upwards of 4% per year.[25,26] This further reveals the importance of a clear and confident diagnosis. The Synovasure Alpha Defensin Lateral Flow Test is therefore recommended as a confirmatory tool to be used in adjunct with the standard of care in all revision THA and TKA cases in order to maximize its potential in reducing the burden of PJI.

Summary

As total joint arthroplasties in the United States continue to rise, PJI is becoming increasingly significant in orthopedics. With such an enormous economic and health related burden associated with treating this complication, accurate diagnosis of PJI is critical. Current SoC tests can have poor sensitivities and/or specificities, and some, such as culture, require extensive turnaround times. The Synovasure Alpha Defensin Lateral Flow Test provides an accurate and rapid result on the presence of alpha defensin to aid in PJI diagnosis and can have high utility as an intraoperative confirmatory tool. The device's potential in reducing economic burden is demonstrated by assuming a reduction in missed infections due to increased diagnostic accuracy when used as an adjunct to the preoperative SoC tests, serum ESR and serum CRP. In an example mid-volume institution, a model based on published sensitivity and specificity levels compared to Serum ESR and Serum CRP predicts the device to save $437,681 in one year. With opportunity to reduce PJI burden, the Synovasure Alpha Defensin Lateral Flow Test could prove to be a vital tool for the future of orthopedics.

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Synovasure Lateral Flow test has been developed for use with synovial fluid only. The use of this test kit with any other specimen type may lead to inaccurate test results.

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