ZIMMER BIOMET

SynTuition™ Score

NAME AND INTENDED USE

SynTuition™ is an Artificial Intelligence/Machine Learning (AI/ML)-based software (SW) available as a laboratory-developed test (LDT) that identifies patients with prior total joint arthroplasty who are being evaluated for peri-prosthetic joint infection (PJI). The SW combines clinical and laboratory variables to generate a **SynTuition™ Score** and assigns the patient to one of three discrete stratification categories: "Low Probability of Infection", "Equivocal", and "High Probability of Infection".

The SynTuition Score is intended to be used in conjunction with other laboratory findings and clinical assessments to aid in the diagnosis of PJI. It is not intended to identify the etiology or severity of the disease.

SynTuition is intended for clinical use only in a qualified clinical diagnostic laboratory. It is not expected that the software will require direct interaction during its operation, hence there isn't a designated primary user for the software itself. The primary User of the SynTuition Score is the healthcare professional who ordered the **Synovasure® Comprehensive PJI Test Panel with SynTuition™ and Culture**.

PRINCIPLES OF THE TEST

SynTuition is a software that utilizes algorithmic analyses to interpret multianalyte assay results from the Synovasure® Comprehensive PJI Test Panel and output a probability of PJI (SynTuition Score) in the patient synovial fluid sample. This multi-analyte diagnostic algorithm requires testing samples for Alpha Defensins 1-3 (AD), C-reactive protein (CRP), microbial antigen (MID) test panel, Total Nucleated Cell Count (TNCC or WBC), percentage of neutrophils (PMN%), red blood cell (RBC) count, and absorbance at 280 nm wavelength (A280).

The AD component of the test panel is an ELISA test based on an immunometric reaction of the Alpha Defensins 1-3 peptides present in the sample. The CRP component consists of antibody-coated latex particles used to capture an immune complex detected on a Beckman Coulter chemistry analyzer. The MID component is a panel of immunometric assays and involves the reaction of the microbial antigen present in the sample with a genus-specific anti-microbial antibody conjugated to MagPlex® microspheres (beads), detected on a Luminex instrument. The MID panel consists of two tests, one of which is a multiplexed assay targeting *staphylococcus* (SPA and SPB), *enterococcus* (EF), and *candida* (CP), and the other which targets *cutibacterium acnes* (PAC). The WBC and RBC counts, as well as PMN%, measurements are performed as standard laboratory tests using a hematology analyzer with manual confirmation of cell counts for samples with WBCs > 3000 cells/µL. The A280 test is a standard spectrophotometric measurement used to verify that the specimen represents synovial fluid that has not been diluted or contaminated. All assays within the test panel are validated for use at CD Laboratories.

The results from each test are interrogated by the SynTuition algorithm to render a probability of PJI, presented as a SynTuition Score. The algorithm incorporates a logistic regression model.

LIMITATION

- SynTuition is restricted to prescription use only.
- Safety and effectiveness of this device have not been evaluated in subjects younger than 18 years of age.

WARNINGS AND PRECAUTIONS

- This test is for in vitro diagnostic use. Test results should be used in conjunction with other clinical and diagnostic findings to aid in the diagnosis of PJI.
- The tests and all assay components should be run by qualified laboratory personnel.
- Synovial fluid modified with saline, blood, contrast agent, or any substances injected into the joint may lead to inaccurate results.
- Follow instructions per Sample Collection & Shipment Instructions (M40035 - Synovasure Comprehensive Infection Panel with SynTuition - Collection & Shipment Instructions)

MATERIALS, SUPPLIES, AND STORAGE CONDITIONS

This software product does not utilize physical materials or supplies for operation. No external standards, calibrators, or quality control materials are required or used with this software product.

For specimen collection and storage, follow instructions per Sample Collection & Shipment Instructions (M40035).

SPECIMEN COLLECTION, PREPARATION, AND STORAGE

Specimen Requirement

Synovial fluid aspirated from a joint.

Specimen Collection and Preparation

Synovial fluid should be collected aseptically by approved medical techniques, then transferred to sterile specimen tubes with no additives (clear top/red stopper) as well as lavender-top tubes containing EDTA and transported at room temperature. Do not use heat-treated specimens. Use the Synovasure® Infection Specimen Transport Kit (00-8888-130-01) to submit the sample. Follow instructions per Sample Collection & Shipment Instructions (M40035).

PROCEDURE

The Synovasure® Comprehensive PJI Test Panel with SynTuition™ and Culture will be requested by healthcare professionals to aid in the diagnosis of infection in patients experiencing joint pain and/or inflammation after total joint arthroplasty, following current practice. A sample of synovial fluid is collected and sent to CD Laboratories, along with the Synovasure® Comprehensive Infection Panel Test Requisition Form (M40036). Trained personnel at CD Laboratories will receive the sample, conduct the tests, and return a report of the test results along with a SynTuition Score to the health care professional.

RESULTS REPORTING

Analytical Measurement Range for SynTuition Score: 1 – 99.

Specimens with a probability outside of the analytical range are reported as <1 or >99.

Clinical Decision Limits for the SynTuition Score:

- >80: High Probability of Infection
- <20: Low Probability of Infection
- 20-80, inclusive: Equivocal
-

PERFORMANCE CHARACTERISTICS

Analytical range

The SynTuition™ Score provides the probability of PJI in synovial fluid with the following analytical range:

SAMPLE TYPE	SYNTUITION SCORE
Synovial Fluid	1 – 99

Samples with the SynTuition Score outside of the analytical range will be reported as "<1" or ">99".

Consult the Instructions for Use (IFU) to determine the analytical range for each assay.

Precision

Consult the Instructions for Use (IFU) to determine the precision for each assay. Input perturbation analysis (IPA) was performed simulating each input component's worst-case performance based on validation data, and the results are provided below.

The following results were observed for the worst-case precision condition where all input components were simulated to their highest imprecision level, except for RBC[1] where it was simulated to its lowest imprecision level. While some samples (1.8%) were re-categorized due to imprecision, most samples (98.2%) remained in the original category, and 0.4% changed from a "low" to a "high" probability of infection. There were no samples that changed from a “high” to a “low” probability of infection. When assessed against the adjudicated modified 2018 International Consensus Meeting (ICM) Criteria, the sensitivity and specificity levels are 98.9% and 96.3%, respectively.

Original SynTuition Score	**SynTuition Score following IPA**		
	<20	**20-80, inclusive**	**>80**
<20	76.5%	0.8%	0.4%
20-80, inclusive	0.0%	0.0%	0.6%
>80	0.0%	0.0%	21.7%

The following results were observed for the worst-case precision condition where all input components were simulated to their lowest imprecision level, except for RBC where it was simulated to its highest imprecision level. While 2.0% of samples were re-categorized due to imprecision, 98.0% of samples remained in the original category, and 0.6% changed from a "high" to a "low" probability of infection. There were no samples that changed from a “low” to a “high” probability of infection. When assessed against the adjudicated modified 2018 ICM Criteria, the sensitivity and specificity levels are 95.4% and 98.7%, respectively.

Original SynTuition Score	**SynTuition Score following IPA**		
	<20	**20-80, inclusive**	**>80**
<20	77.7%	0.0%	0.0%
20-80, inclusive	0.6%	0.0%	0.0%
>80	0.6%	0.8%	20.3%

Interfering substances

Consult the Instructions for Use (IFU) to determine the interfering substances for each input component, as this may impact the accuracy of the SynTuition Score. Based on the worst-case interference data from the validation studies of the input components, the following conditions were tested, and the results are presented below. All conditions demonstrated sensitivity and specificity above 95%. The highest discordance rate, defined as a change from one stratification category to another, was 0.6%. No samples shifted from “High” to “Low” probability of infection or vice versa, so discordance was due to samples shifting into and out of the equivocal range.

[1] Since the logistic regression coefficient for RBC is negative, unlike the positive coefficients of the other input components, the worst-case scenario occurs when this input is perturbed in the opposite direction to the others.

Input Component	Interference Effect (% Baseline)	Sensitivity	Specificity	% Discordant ("High" to "Low", vice versa)	% Total Discordant
CRP	90.9	98.0%	97.7%	0.0	0.1
AD	83.3	97.6%	97.9%	0.0	0.5
TNCC	94.1	98.0%	97.7%	0.0	0.1
SPA	82.1	97.7%	97.8%	0.0	0.4
SPA	112.5	98.3%	97.5%	0.0	0.3
SPB	90.0	97.9%	97.7%	0.0	0.1
SPB	120.0	98.4%	97.5%	0.0	0.3
CP	120.0	98.1%	97.6%	0.0	0.0
EF	83.3	97.6%	97.9%	0.0	0.6
EF	120.0	98.5%	97.3%	0.0	0.6

Limit of Detection (LoD)

Consult the Instructions for Use (IFU) to determine the detection limits for each input component. The SynTuition Score was generated after truncating the lower-end signals for the applicable assay components to their respective LoD, and the results are presented below. All conditions demonstrated sensitivity and specificity above 95%. The highest discordance rate, defined as a change from one stratification category to another, was 0.78%. No samples shifted from "High" to "Low" probability of infection or vice versa, so discordance was due to samples shifting into and out of the equivocal range.

Input Component	LoD (S/CO)	Sensitivity	Specificity	% Discordant ("High" to "Low", vice versa)	% Total Discordant
AD	0.11	98.1%	97.6%	0.0	0.0
SPA	0.74	98.1%	97.6%	0.0	0.1
SPB	0.67	98.3%	97.5%	0.0	0.3
CP	0.49	98.1%	97.6%	0.0	0.0
EF	0.54	98.1%	97.6%	0.0	0.1
PAC	0.55	98.5%	97.2%	0.0	0.8

Clinical Performance

The modified 2018 International Consensus Meeting (ICM) Criteria were used to establish and validate positive and negative cutoffs for PJI. The 2018 ICM Criteria was modified by substituting serum CRP with synovial fluid CRP at a threshold of 4.45 mg/L.[14]

A subset of 83,272 samples, constituting 80% of the overall dataset, was utilized to develop the algorithm and establish optimal cutoffs. This subset comprised 15,302 (18.4%) identified as Infected, 62,130 (74.6%) as Not Infected, and 5,840 (7.0%) as Inconclusive, as classified by the modified 2018 ICM Criteria. The SynTuition Score cutoffs at <20 and >80 were determined for the "Low Probability of Infection" and "High Probability of Infection" clinical decision limits, respectively. SynTuition Scores between 20 and 80 (inclusive) were considered Equivocal.

Subsequently, the cutoffs were validated using the remaining 20,818 subjects (20%) of the dataset. This subset comprised 3,779 (18.2%) identified as Infected, 15,597 (74.9%) as Not Infected, and 1,442 (6.9%) as Inconclusive per the modified 2018 ICM. Sensitivity and specificity were demonstrated to be 99.3% (95% CI: 99.0% - 99.5%) and 99.5% (95% CI: 99.4% - 99.6%), respectively, when the ICM Inconclusive cohort was excluded from the analysis. When the ICM Inconclusive cohort was reclassified by an internal adjudication process into either Infected or Not Infected categories, sensitivity and specificity were found to be 98.1% (95% CI: 97.6% - 98.4%) and 97.6% (95% CI: 97.4% - 97.9%), respectively. All sensitivity and specificity assessments were performed assuming the worst-case scenario where the

Equivocal cohort (0.6%) was included in the false-negative determination for sensitivity and false-positive determination for specificity. When assessed at the adjudicated disease prevalence of 20.7%, the positive predictive value (PPV) and negative predictive value (NPV) were 91.5% and 99.5%, respectively.

REFERENCES

1. M40003 Synovasure Alpha Defensin ELISA Test IFU
2. IM: 710 Specimen Integrity Test
3. M40022 Synovasure Microbial ID Test IFU
4. M40023 Synovasure Microbial ID P acnes Test IFU
5. LP1003 AU480 CRP Synovasure IFU
6. HE: 201 Sysmex XN-350 Automated Hematology Analyzer
7. HE: 205 Manual Total Nucleated Cell Count for Synovial Fluid
8. 12516-023R SynTuition Design and Development Report
9. 12516- 028R SynTuition Input Perturbation Analysis Design Verification Report
10. 12516-032R SynTuition Clinical Validation Report
11. 12516-022M Adjudication Rules Tech Memo
12. M40035 Collection & Shipment Instructions
13. M40036 Synovasure® Comprehensive Infection Panel Test Requisition Form
14. Miamidian, J. L., Toler, K., McLaren, A., & Deirmengian, C. (2024). Synovial fluid C-reactive protein clinical decision limit and diagnostic accuracy for periprosthetic joint infection. *Cureus*, *16*(1).

REVISION HISTORY

Version	Effective Date	Changes made from the previous version
1	November 2025	• Initial Release