April 2, 2024

Prenosis, Inc.
% Isabella Schmitt
Director of Regulatory Affairs
Proxima Clinical Research
2450 Holcombe Blvd
Houston, Texas 77021

Re: DEN230036
Trade/Device Name: Sepsis ImmunoScore
Regulation Number: 21 CFR 880.6316
Regulation Name: Software device to aid in the prediction or diagnosis of sepsis
Regulatory Class: Class II
Product Code: SAK
Dated: May 4, 2023
Received: May 5, 2023

Dear Isabella Schmitt:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the Sepsis ImmunoScore, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> The Sepsis ImmunoScore is an Artificial Intelligence/Machine Learning (AI/ML)-Based Software that identifies patients at risk for having or developing sepsis.
>
> The Sepsis ImmunoScore uses up to 22 predetermined inputs from the patient's electronic health record to generate a risk score and to assign the patient to one of four discrete risk stratification categories, based on the increasing risk of sepsis.
>
> The Sepsis ImmunoScore is intended to be used in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment for presence of or progression to sepsis within 24 hours of patient assessment. It is intended to be used for patients admitted to the Emergency Department or hospital for whom sepsis is suspected, and a blood culture was ordered as part of the evaluation for sepsis. It should not be used as the sole basis to determine the presence of sepsis or risk of developing sepsis within 24 hours.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Sepsis ImmunoScore, and substantially equivalent devices of this generic type, into Class II under the generic name software device to aid in the prediction or diagnosis of sepsis.

FDA identifies this generic type of device as:

> **Software device to aid in the prediction or diagnosis of sepsis.** A software device to aid in the prediction or diagnosis of sepsis uses advanced algorithms to analyze patient specific data to aid health care providers in the prediction and/or diagnosis of sepsis. The device is intended for adjunctive use and is not intended to be used as the sole determining factor in assessing a patient's sepsis status. The device may contain alarms that alert the care provider of the patient's status. The device is not intended to monitor response to treatment in patients being treated for sepsis.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On May 5, 2023, FDA received your De Novo requesting classification of the Sepsis ImmunoScore. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Sepsis ImmunoScore into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, FDA has determined that, for the previously stated indications for use, the Sepsis ImmunoScore can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Risks to Health	**Mitigation Measures**
Algorithm failure leading to categorizing patient either in a higher risk category resulting in unnecessary treatment or in a lower risk category resulting in delayed or ineffective treatment	Clinical performance testing Non-clinical performance testing Post-market management Software verification, validation, and hazard analysis Labeling
Ineffective treatment or diagnosis due to model bias or failure to adequately generalize to the intended use population	Clinical performance testing Labeling Post-market management

Risks to Health	Mitigation Measures
Overreliance on the device or incorrect interpretation of device results by end user leading to ineffective patient management	Human factors assessment Labeling Technological characteristics
Inadequate input data quality, missing inputs, or unsupported input/hardware leading to delayed or ineffective treatment	Clinical performance testing Non-clinical performance testing Software verification, validation, and hazard analysis Labeling Post-market management

In combination with the general controls of the FD&C Act, the software device to aid in the prediction or diagnosis of sepsis is subject to the following special controls:

(1) Clinical performance testing must demonstrate the performance characteristics of the device under anticipated conditions of use across the intended use population. The following must be met:
   (i) Validation must use a clinical test dataset acquired from a representative patient population. Data must be representative of the range of data sources and data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment;
   (ii) Establishment of ground truth (reference method or clinical comparator) must be clinically justified. Study protocols must include a description of the adjudication process(es) for determining ground truth of training and test datasets;
   (iii) Testing must compare device performance to a ground truth and report objective performance measures (e.g., sensitivity, specificity, positive predictive value, negative predictive value, or likelihood ratios) with relevant descriptive or developmental performance measures. Summary level demographic information for study subjects and clinicians must be provided. Sub-group analyses for specific predictive or diagnostic indications, study sites, relevant demographic sub-groups, and acquisition systems must be provided;
   (iv) Performance goals used to determine success of clinical validation must be clinically justified;
   (v) The dataset used for training and development of the advanced algorithm must be distinct from the dataset used for testing to support generalizability of the algorithm; and
   (vi) All adverse events must be reported.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including:
   (i) Precision/sensitivity range of input parameters;
   (ii) Reproducibility of the outputs based on perturbations to the inputs;
   (iii) Missing input analysis (e.g., feature imputation study); and
   (iv) Monotonicity of any device outputs presented as risk scores.

(3) Software verification, validation, and hazard analysis must be provided.

(4) Human factors assessment must demonstrate that the intended user(s) can safely and correctly use the device and interpret the results in the intended use environment.

(5) Device technological characteristics must specify that the presentation of outputs in the user interface must be accompanied by information necessary to interpret the output, including labeling requirements in paragraph 6(i) to 6(iii) of this section.
(6) Labeling must include:
  (i) A summary of the development data and clinical validation data, including sources of data, study sites, samples sizes, demographics and other relevant characteristics of the study participants (including age, gender, race or ethnicity, and patient condition), and a description of the ground truth;
  (ii) A summary of clinical validation results, and information on subpopulations (age, gender, race, or ethnicity) that may experience disparate performance, and a description of the ground truth;
  (iii) A detailed description of the device inputs and outputs and how to interpret outputs;
  (iv) Hardware platform and operating system requirements;
  (v) Situations in which the device may not operate at an expected performance level;
  (vi) A statement that the device output should not be used as the sole basis to determine the presence of sepsis or risk of developing sepsis; and
  (vii) A statement that the device is not intended to be used for monitoring of patient response to treatment.
(7) The device manufacturer must develop and implement a post-market performance management plan that ensures regular assessment of the generalizability and device performance in the intended patient population in real-world use. The plan must include:
  (i) Data collection, analysis methods, and procedures for:
    (A) Monitoring relevant performance characteristics and detecting changes in performance;
    (B) Identifying sources of performance changes between validation and the real-world environment over time; and
    (C) Assessing the results from the performance monitoring on safety and effectiveness.
  (ii) Procedures for communicating the device's current performance to users.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the software device to aid in the prediction or diagnosis of sepsis they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act; 21 CFR 1000-1050).

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Sivakami Venkatachalam at 301-796-9103.

Sincerely,

Kellie B. Kelm -S

Kellie B. Kelm, Ph.D.
Acting Office Director
OHT3: Office of GastrorRenal, ObGyn,
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