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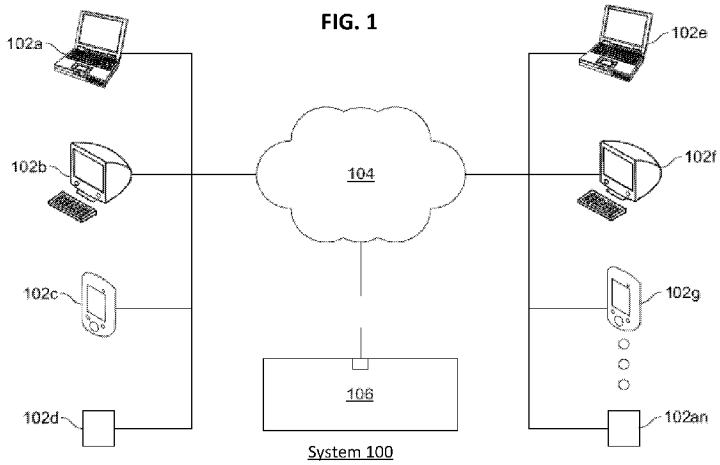
(54) Title: USE OF CLINICAL PARAMETERS FOR THE PREDICTION OF SIRS

FIG. 1



(57) Abstract: A system for disease prediction includes processing circuitry configured to receive a dataset including data of a patient population, the data including for each of a plurality of patients of the patient population, values for a plurality of features, and a diagnosis value indicating whether a disease has been diagnosed. The processing circuitry is configured to, based on correlations between the values, select from the dataset a plurality of subsets of the features, and, for each of at least one of the subsets, execute a machine learning process with the respective subset and the diagnosis values as input parameters, the execution generating a respective prediction model. The processing circuitry is configured to output the respective prediction model.

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USE OF CLINICAL PARAMETERS FOR THE PREDICTION OF SIRS

FIELD OF THE INVENTION

The present invention relates to the composition and use of clinical parameters for the prediction, or risk stratification for Systemic Inflammatory Response Syndrome (SIRS) several hours to days before SIRS symptoms are observable for a definitive diagnosis in a patient. The ability to predict the onset of SIRS, prior to the appearance of clinical symptoms, enables physicians to initiate therapy in an expeditious manner, thereby improving outcomes. This applies to patients that have non-infectious SIRS or patients with SIRS that progress to sepsis. The present invention is also directed to a method of determining parameters and combinations thereof, which are relevant for predicting onset of a disease, e.g., SIRS.

DISCUSSION

A biomarker is a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure. For example, detection of a cancer-associated protein biomarker in the blood means the patient already has cancer. Pursuant to this invention, however, a combination of clinical features or parameters such as physiologic and/or clinical procedures (e.g., PO2 or Fingerstick Glucose) is used to predict how likely the patient will progress to SIRS. These features are noted as part of a patient's health records, but are not previously associated with SIRS prior to this invention.

Prior published work related to the application of artificial intelligence and/or biomarker approaches to sepsis was designed mainly to improve the sensitivity and specificity of sepsis diagnosis at various stages of the progressive syndrome. Thus, the studies involved were conducted in patients, mainly in intensive care units, for whom a diagnosis of sepsis had already been made, based on widely accepted clinical criteria. In contrast, the invention predicts the onset of SIRS, prior to the appearance of clinical symptoms, which the invention has accomplished in intensive care patients with a sensitivity of 85–95%, an accuracy of 80–85%, and area under the curve (AUC) of 0.70–0.85. One of ordinary skill in the art would readily understand the meaning of the foregoing terms, which are standard in the machine learning literature and are well known to one of ordinary skill in the art. The present invention advantageously uses algorithms to analyze the types of available clinical and laboratory data that are normally collected in hospital patients to make its predictions, without requiring blood sampling and analysis for specific biomarkers.

SIRS

SIRS, Systemic Inflammatory Response Syndrome, is a whole-body inflammatory state. A mild systemic inflammatory response to any bodily insult may normally have some salutatory effects. However, a marked or prolonged response, such as that associated with severe infections, is often deleterious and can result in widespread organ dysfunction. Many infectious agents are capable of inducing SIRS. These organisms either elaborate toxins or stimulate release of substances that trigger this response. Commonly recognized initiators are the lipopolysaccharides (LPSs, sometimes referred to as endotoxin), that are released by gram-negative bacteria. The resulting response involves a complex interaction between macrophages/monocytes, neutrophils, lymphocytes, platelets, and endothelial cells that can affect nearly every organ. *Infectious* SIRS can occur as a result of the following pathologic conditions: bacterial sepsis; burn and wound infections; candidiasis; cellulitis; cholecystitis; pneumonia; diabetic foot infection; infective endocarditis; influenza; intra-abdominal infections (e.g., diverticulitis, appendicitis); meningitis; colitis; pyelonephritis; septic arthritis; toxic shock syndrome; and urinary tract infections.

While SIRS can lead to sepsis, SIRS is not exclusively related to infection. Its etiology is broad and includes noninfectious conditions, surgical procedures, trauma, medications, and therapies. Some examples of conditions associated with *non-infectious SIRS* include: acute mesenteric ischemia; adrenal insufficiency; autoimmune disorders; burns; chemical aspiration; cirrhosis; dehydration; drug reaction; electrical injuries; hemorrhagic shock; hematologic malignancy; intestinal perforation; medication side effect; myocardial infarction; pancreatitis; seizure; substance abuse; surgical procedures; transfusion reactions; upper gastrointestinal bleeding; and vasculitis.

SIRS has been clinically defined as the simultaneous presence of two or more of the following features in adults: body temperature >38°C (100.4°F) or <36°C (96.8°F); heart rate of >90 beats per minute; respiratory rate of >20 breaths per minute or arterial carbon dioxide tension (P_aCO_2) of <32 mm Hg; and abnormal white blood cell count (>12,000/μL or < 4,000/μL or >10% immature [band] forms).

Pathophysiology of SIRS

The complex pathophysiology of SIRS is independent of etiologic factors, with minor differences with respect to the cascades that it incites. This pathophysiology is briefly outlined as follows. Inflammation, the body's response to nonspecific insults that arise from chemical, traumatic, or infectious stimuli is a critically important component. The inflammation itself is a process involving humoral and cellular responses, complement, and cytokine cascades. The

relationship between these complex interactions and SIRS has been defined as a three-stage process. *See* Bone et al. (1992) (all citations refer to references listed at the end of the document).

In stage 1, following an insult cytokines are produced at the site. Local cytokine production incites an inflammatory response, thereby promoting wound repair and recruitment of the reticular endothelial (fixed macrophage) system. This process is essential for normal host defense homeostasis, and its malfunction is life-threatening. Local inflammation, such as in the skin and subcutaneous soft tissues, carries the classic description of *rubor* (redness), *tumor* (swelling), *dolor* (pain), *calor* (increased heat) and *functio laesa* (loss of function). Importantly, on a local level, this cytokine and chemokine release may cause local tissue destruction or cellular injury by attracting activated leukocytes to the region.

In stage 2, small quantities of local cytokines are released into the circulation, enhancing the local response. This leads to growth factor stimulation and the recruitment of macrophages and platelets. This acute phase response is typically well-controlled by a decrease in pro-inflammatory mediators and by the release of endogenous antagonists.

In stage 3, a significant systemic reaction occurs if the inflammatory stimuli continue to spread into the systemic circulation. The cytokine release leads to destruction rather than protection. A consequence of this is the activation of numerous humoral cascades, generalized activation of the reticular endothelial system, and subsequent loss of circulatory integrity. This leads to end-organ dysfunction.

When SIRS is mediated by an infectious insult, the inflammatory cascade is often initiated by endotoxin. Tissue macrophages, monocytes, mast cells, platelets, and endothelial cells are able to produce a multitude of cytokines. The cytokines tissue necrosis factor–alpha (TNF-α) and interleukin-1 (IL-1) are released first and initiate several downstream cascades.

The release of IL-1 and TNF-α (or the presence of endotoxin) leads to cleavage of the nuclear factor NF-kappa B (NF-κB) inhibitor. Once the inhibitor is removed, NF-κB initiates expression of mRNAs encoding genes regulating production of other pro-inflammatory cytokines, primarily IL-6, IL-8, and interferon gamma. TNF- α and IL-1 have been shown to be released in large quantities within 1 hour of an insult and have both local and systemic effects. TNF-α and IL-1 are responsible for fever and the release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system).

Other cytokines, especially IL-6, stimulate the release of acute-phase reactants such as C-reactive protein (CRP) and procalcitonin. Notably, infection has been shown to induce a

greater release of TNF-α, thus inducing a greater release of IL-6 and IL-8 than trauma does. This is suggested to be the reason higher fever is associated with infection rather than trauma.

The pro-inflammatory interleukins either function directly on tissue or via secondary mediators to activate the coagulation cascade and the complement cascade as well as the release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes. HMGB1 (high mobility group box 1) is a protein present in the cytoplasm and nuclei in a majority of cell types. It acts as a potent pro-inflammatory cytokine and is involved in delayed endotoxin lethality and sepsis. In response to infection or injury, as is seen with SIRS, HMGB1 is secreted by innate immune cells and/or released passively by damaged cells. Thus, elevated serum and tissue levels of HMGB1 are induced by many of the agents that cause SIRS.

A correlation that exists between inflammation and coagulation is critical to the progression of SIRS. IL-1 and TNF-α directly affect endothelial surfaces, leading to the expression of tissue factor. Tissue factor initiates the production of thrombin, thereby promoting coagulation, and is a pro-inflammatory mediator itself. Fibrinolysis is impaired by IL-1 and TNF-α via production of plasminogen activator inhibitor-1. Pro-inflammatory cytokines also disrupt the naturally occurring anti-inflammatory mediators, anti-thrombin and activated protein-C (APC). If unchecked, this coagulation cascade leads to complications resulting from microvascular thrombosis, including organ dysfunction. The complement system also plays a role in the coagulation cascade. Infection-related pro-coagulant activity is generally more severe than that produced by trauma.

The cumulative effect of this inflammatory cascade is an unbalanced state, with inflammation and coagulation dominating. To counteract the acute inflammatory response, the body is equipped to reverse this process via the counter-inflammatory response syndrome (CARS). IL-4 and IL-10 are cytokines responsible for decreasing the production of TNF-α, IL-1, IL-6, and IL-8. The acute phase response also produces antagonists to TNF-α and IL-1 receptors. These antagonists either bind the cytokine, and thereby inactivate it, or block the receptors. The balance of SIRS and CARS helps to determine a patient's outcome after an insult.

The normal physiology of an inflammatory response consists of an acute pro-inflammatory state resulting from innate immune system recognition of ligands, and an anti-inflammatory phase that can serve to modulate the pro-inflammatory phase. Under normal circumstances, these coordinated responses direct a return to homeostasis. Severe or protracted SIRS can result in septic shock. Bacteremia is usually present but may be absent. Increased nitric oxide levels may be responsible for vasodilation, and hypotension is also due to decreased circulating

intravascular volume resulting from diffuse capillary leaks. Activation of platelets and the coagulation cascade can lead to the formation of fibrin- platelet aggregates, which further compromise tissue blood flow. The release of vasoactive substances, formation of microthrombi in the pulmonary circulation, or both together increase pulmonary vascular resistance, whereas systemic venodilation and transudation of fluid into tissues result in relative hypovolemia.

Epidemiology of SIRS

The true incidence of SIRS is unknown but probably much higher than documented, owing to the nonspecific nature of its definition. Not all patients with SIRS require hospitalization or have diseases that progress to serious illness. Because SIRS criteria are nonspecific and occur in patients who present with conditions ranging from influenza to cardiovascular collapse associated with severe pancreatitis, it is useful to stratify any incidence figures based on SIRS severity.

Results of epidemiologic studies conducted in the US have been published. A prospective survey of patients admitted to a tertiary care center revealed that 68% of hospital admissions to surveyed units met SIRS criteria. *See* Rangel-Fausto et al. (1995). The incidence of SIRS increased as the level of unit acuity increased. The following progression of patients *with SIRS* was noted: 26% developed sepsis, 18% developed severe sepsis, and 4% developed septic shock within 28 days of admission.

A hospital survey of SIRS revealed an overall in-hospital incidence of 542 episodes per 1000 hospital days. *See* Pittet et al. (1995). In comparison, the incidence in the intensive care unit (ICU) was 840 episodes per 1000 hospital days. Another study demonstrated that 62% of patients who presented to the emergency department with SIRS had a confirmed infection, while 38% did not. *See* Comstedt et al. (2009). Still, the incidence of severe SIRS associated with infection was found to be 3 cases per 1,000 population, or 2.26 cases per 100 hospital discharges. *See* Angus et al. (2001). The real incidence of SIRS, therefore, must be much higher and depends significantly on the rigor with which the definition is applied.

Prognosis of SIRS Patients

Prognosis depends on the etiologic source of SIRS, as well as on associated comorbidities. A study of SIRS in acutely hospitalized medical patients demonstrated a 6.9 times higher 28-day mortality in SIRS patients than in non-SIRS patients. Most deaths occurred in SIRS patients with an associated malignancy. *See* Comstedt et al. (2009). Mortality rates in the study of tertiary care patients mentioned above, *see* Rangel-Fausto et al. (1995), were 7% (SIRS), 16% (sepsis), 20% (severe sepsis), and 46% (septic shock). The median time interval

from SIRS to sepsis was inversely related to the number of SIRS criteria met. Morbidity was related to the causes of SIRS, complications of organ failure, and the potential for prolonged hospitalization. A study evaluating mortality in patients with suspected infection in the emergency department showed the following in-hospital mortality rates: Suspected infection without *SIRS*, 2.1%; *Sepsis*, 1.3%; *Severe Sepsis*, 9.2%; and *Septic Shock*, 28%. *See* Shapiro et al. (2006).

Evaluation of the *SIRS* criteria in patients who underwent transcatheter aortic valve implantation (TAVI) revealed that *SIRS* appeared to be a strong predictor of mortality. *See* Sinning et al. (2012). The occurrence of *SIRS* was characterized by a significantly elevated release of IL-6 and IL-8, with subsequent increase in the leukocyte count, C-reactive protein (CRP), and pro-calcitonin. The occurrence of SIRS was related to 30-day and 1-year mortality (18% vs 1.1% and 52.5% vs 9.9%, respectively) and independently predicted 1-year mortality risk.

The early identification and administration of supportive care is key in the management of patients with SIRS who could progress to Sepsis, Severe Sepsis or Septic Shock. Several studies have shown that fluids and antibiotics, when administered early in the disease process, can prevent hypoxemia and hypotension. *See* Annane et al. (2005); Dellinger et al. (2008); Hollenberg et al. (2004); and Dellinger et al. (2013). Indeed, international guidelines on the management of sepsis recommend the initiation of resuscitative measures within 6 hours of the recognition of septic symptoms. *See* Dellinger et al. (2013).

The ability to predict the onset of SIRS, prior to the appearance of clinical symptoms would enable physicians to initiate therapy in an expeditious manner, thereby improving outcomes. This applies to patients that have non-infectious SIRS or patients with SIRS that progress to Sepsis.

SIRS is associated with a variety of inflammatory states, including sepsis, pancreatitis, burns, surgery, etc. When confronted with SIRS, physicians typically attempt to identify potential etiologies and interventions that can prevent adverse outcomes. For example, sepsis is a frequently encountered problem in intensive care unit (ICU) patients who have been instrumented with invasive catheters. Since SIRS precedes sepsis, and the development of sepsis is associated with significant morbidity and mortality, the presence of SIRS in the ICU cannot be ignored. SIRS in these patients often prompts a search for a focus of infection and potentially the administration of empiric antibiotics. Since minimizing the time to antibiotic administration is one intervention that has consistently been shown to improve outcomes in

these patients, SIRS often serves as an alarm that causes health care workers to consider the use of antimicrobials in selected patients.

However, using the invention to predict the onset of SIRS 6 to 48 hours earlier (e.g., 6, 12, 24 or 48 hours earlier) would allow one to administer antibiotics earlier, with advantages either because the patients would not get as sick initially, before they get better, or because there is time to try one more antibiotic if the first one or two (or more) do not work. In patients with bacteremia, SIRS often portends the development of sepsis, severe sepsis and/or septic shock. It is important to recognize that in these patients SIRS is diagnosed *after* the patient has already been infected. Methods that identify patients who will eventually develop SIRS are desirable because they detect patients who are at an earlier stage in the infectious process. The key benefit of early and accurate SIRS prediction is the ability to identify patients who are at risk of infection *before* the infection has started to manifest itself. Since there are a great deal of data to suggest that the earlier supportive therapy is administered (e.g., fluid and antibiotics), the better the outcomes, a SIRS prediction prior to the onset of symptoms could significantly impact clinical management and outcomes. More precisely, the accurate prediction of SIRS 6 to 48 (e.g., 6, 12, 24 or 48) hours prior to the onset of symptoms would provide enough time to mobilize hospital resources, creating the best environment for the patient. For example:

Patients on inpatient floors who are identified as being at high risk of SIRS could be transferred to high acuity units that have a higher nurse-to-patient ratio, thereby helping to ensure that such patients are monitored in a manner that is commensurate with their risk;

A positive SIRS prediction in patients who are instrumented with invasive catheters (which on its own may increase one's risk of bacteremia) would warrant closer monitoring for septic signs, and potentially a search for a septic focus. The threshold for the administration of fluids and empiric antibiotics in these patients would be significantly lower than patients who have not been identified as high risk; and

Patients who are identified as being at high risk for SIRS would benefit from a careful review of their medication history to ensure that they are not on agents that may be associated with a drug reaction (a cause of non-infectious SIRS). Careful review of medications in such patients provides one mechanism to circumvent adverse medication side effects.

BIOMARKERS IN THE DIAGNOSIS OF SIRS

The role of biomarkers in the diagnosis of sepsis and patient management has been evaluated. *See* Bernstein (2008). SIRS is an acute response to trauma, burn, or infectious injury characterized by fever, hemodynamic and respiratory changes, and metabolic changes,

not all of which are consistently present. The SIRS reaction involves hormonally driven changes in liver glycogen reserves, triggering of lipolysis, lean body proteolysis, and reprioritization of hepatic protein synthesis with up-regulation of synthesis of acute phase proteins and down-regulation of albumin and important circulating transport proteins. Understanding of the processes has led to the identification of biomarkers for identification of sepsis and severe, moderate or early SIRS, which also can hasten treatment and recovery. The SIRS reaction unabated leads to a recurring cycle with hemodynamic collapse from septic shock, indistinguishable from cardiogenic shock, and death.

By focusing on early and accurate diagnosis of infection in patients suspected of SIRS, antibiotic overuse and its associated morbidity and mortality may be avoided, and therapeutic targets may be identified. The performance of diagnostic algorithms and biomarkers for sepsis in patients presenting with leukocytosis and other findings has been evaluated. Suspected patients are usually identified by WBC above 12,000/Ml, procalcitonin level, SIRS and other criteria, such as serum biomarkers of sepsis. In a study of 435 patients, *see* Gultepe et al. (2014), procalcitonin alone was a superior marker for sepsis. In patients with sepsis there was a marked increase in procalcitonin ($p = 0.0001$), and in patients requiring ICU admission, heart rate and blood pressure monitoring, and assisted ventilation were increased ($p = 0.0001$).

The emergence of large-scale data integration in electronic health records (EHR) presents unprecedented opportunities for design of methods to construct knowledge from heterogeneous datasets, and as an extension, to inform clinical decisions. However, current ability to efficiently extract informed decision support is limited due to the complexity of the clinical states and decision process, missing data and lack of analytical tools to advise based on statistical relationships. A machine learning basis for a clinical decision support system to identify patients at high risk for hyperlactatemia based upon routinely measured vital signs and laboratory studies has been developed. *See* Gultepe et al. (2014).

Electronic health records of 741 adult patients who met at least two systemic inflammatory response syndrome (SIRS) criteria were used to associate patients' vital signs, white blood cell count (WBC), with sepsis occurrence and mortality. Generative and discriminative classification (naïve Bayes, support vector machines, Gaussian mixture models, hidden Markov models) were used to integrate heterogeneous patient data and form a predictive tool for the inference of lactate level and mortality risk.

An accuracy of 0.99 and discriminability of 1.00 area under the receiver operating characteristic curve (AUC) for lactate level prediction was obtained when the vital signs and WBC measurements were analyzed in a 24 h time bin. An accuracy of 0.73 and discriminability

of 0.73 AUC for mortality prediction in patients with sepsis was achieved with three properties: median of lactate levels, mean arterial pressure, and median absolute deviation of the respiratory rate. These findings introduce a new scheme for the prediction of lactate levels and mortality risk from patient vital signs and WBC. Accurate prediction of both these variables can drive the appropriate response by clinical staff. *See* Gultepe et al. (2014).

SEPSIS

Sepsis is one of the oldest syndromes in medicine. It is the leading cause of death in non-coronary ICUs in the US, with associated mortality rates upwards of 80%. *See* Shapiro et al. (2006); Sinning et al. (2012); and Nierhaus et al. (2013). The term *Sepsis* refers to a clinical spectrum of complications, often starting with an initial infection. Untreated, the disease cascade progresses through stages with increasing mortality, from S*IRS* to *Sepsis* to *Severe Sepsis* to *Septic Shock,* and ultimately death. *See* Shapiro et al. (2006); Sinning et al. (2012); Nierhaus et al. (2013); and Lai et al. (2010). A representative course is illustrated in a prospective study that found 36% mortality in ICU patients with *Sepsis*, 52% in patients with *Severe Sepsis* and 82% in patients with *Septic Shock*. *See* Jekarl et al. (2013). While early goal-directed therapy has been shown to provide substantial benefits in patient outcomes, efficacy is contingent upon early detection or suspicion of the underlying septic etiology.

In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to infection, noting that sepsis could arise in response to multiple infectious causes. The panel proposed the term “severe sepsis” to describe instances in which sepsis is complicated by acute organ dysfunction, and they codified “septic shock” as sepsis complicated by either hypotension that is refractory to fluid resuscitation or by hyperlactatemia. In 2003, a second consensus panel endorsed most of these concepts, with the caveat that signs of SIRS, such as tachycardia or an elevated white-cell count, occur in many infectious and noninfectious conditions and therefore are not helpful in distinguishing sepsis from other conditions. Thus, “severe sepsis” and “sepsis” are sometimes used interchangeably to describe the syndrome of infection complicated by acute organ dysfunction. *See* Angus et al. (2013).

These definitions have achieved widespread usage and become the gold standard in sepsis protocols and research. Yet sepsis clearly comprises a complex, dynamic, and relational distortion of human life. Given the profound scope of the loss of life worldwide, a need has been expressed to disengage from the simple concepts of the past and develop new approaches which engage sepsis in its true form, as a complex, dynamic, and relational pattern of death. *See* Lawrence A. Lynn (2014).

BIOMARKERS IN DIAGNOSIS OF SEPSIS

Several molecular markers have been discussed to facilitate diagnosis and treatment monitoring of sepsis in humans and several animal species. The most widely used ones may be CRP (C-reactive protein) and PCT (procalcitonin). Also various interleukins have been discussed as potential biomarkers of sepsis. However they are of limited use at present because of a lack of specificity. For example, Carrigan et al. (2004) reported that sensitivities and specificities for these markers in humans, in whom septic disease patterns have been extensively investigated, sensitivity and specificity of current markers can (even as mean values) be as low as 33% and 66%, respectively. Published data also have a high degree of inhomogeneity. Thus, there is a definite need for new diagnostic markers with improved diagnostic characteristics for the diagnosis of sepsis, especially early diagnosis. In systemic inflammation, i.e. in multiply traumatized patients, such a diagnosis is often very difficult because of other pathological processes interfering with the "normal" physiological values and parameters measured in standard intensive care medicine. Diagnosis of sepsis in patients with systemic inflammation, e. g. complications in polytraumatised patients, is a specific problem for which a high need exists in intensive care medicine.

Biomarkers for sepsis and resulting mortality can be detected by assaying blood samples. Changes in the concentration of the biomarkers can be used to indicate sepsis, risk of sepsis, progression of sepsis, remission from sepsis, and risk of mortality. Changes can be evaluated relative to datasets, natural or synthetic or semisynthetic control samples, or patient samples collected at different time points. Some biomarkers' concentrations are elevated during disease and some are depressed. These are termed informative biomarkers. Some biomarkers are diagnostic in combination with others. Individual biomarkers may be weighted when used in combinations. Biomarkers can be assessed individually, isolated or in assays, in parallel assays, or in single-pot assays. *See* the '982 patent.

The early prediction or diagnosis of sepsis allows for clinical intervention before the disease rapidly progresses beyond initial stages to the more severe stages, such as severe sepsis or septic shock, which are associated with high mortality. Prediction or diagnosis has been accomplished, *see* the '573 patent, using a molecular diagnostics approach, involving comparing an individual's profile of biomarker expression to profiles obtained from one or more control, or reference, populations, which may include a population who develops sepsis. Recognition of features in the individual's biomarker profile that are characteristic of the onset of sepsis allows a clinician to diagnose the onset of sepsis from a bodily fluid isolated from the individual at a single point in time. The necessity of monitoring the patient over a period of

time may be avoided, allowing clinical intervention before the onset of serious symptoms. Further, because the biomarker expression is assayed for its profile, identification of the particular biomarkers is unnecessary. The comparison of an individual's biomarker profile to biomarker profiles of appropriate reference populations likewise can be used to diagnose SIRS in the individual. *See* the '573 patent.

Additional biomarkers for the diagnosis of sepsis include detection of inducible nitric oxide (NO) synthase (the enzyme responsible for overproduction of NO in inflammation), detection of endotoxin neutralization, and patterns of blood proteins. A panel of blood biomarkers for assessing a sepsis condition utilizes an iNOS indicator in combination with one or more indicators of patient predisposition to becoming septic, the existence of organ damage, or the worsening or recovering from a sepsis episode. *See* the '968 publication. Endotoxin neutralization as a biomarker for sepsis has been demonstrated, *see* the '530 publication, using methods specifically developed for detecting the neutralization in a human subject. This system has also provided methods for determining the effectiveness of a therapeutic agent for treating sepsis. *See* the '530 publication. Application of modern approaches of global proteomic has been used for the identification and detection of biological fluid biomarkers of neonatal sepsis. *See* the '652 publication. Methods using expression levels of the biomarkers Triggering Receptor Expressed on Myeloid cells-1 (TREM 1) and TREM-like receptor transcript-1 (TLT1) as an indication of the condition of the patient, alone or in combination with further sepsis markers have been used for the diagnosis, prognosis and prediction of sepsis in a subject. *See* the '370 patent. When levels of the biomarkers indicate the presence of sepsis, treatment of the patient with an antibiotic and/or fluid resuscitation treatment is indicated. *See* the '370 patent.

A multibiomarker-based outcome risk stratification model has been developed for adult septic shock. *See* the '869 publication. The approach employs methods for identifying, validating, and measuring clinically relevant, quantifiable biomarkers of diagnostic and therapeutic responses for blood, vascular, cardiac, and respiratory tract dysfunction, particularly as those responses relate to septic shock in adult patients. The model consists of identifying one or more biomarkers associated with septic shock in adult patients, obtaining a sample from an adult patient having at least one indication of septic shock, then quantifying from the sample an amount of one or more biomarkers, wherein the level of the biomarker(s) correlates with a predicted outcome. *See* the '869 publication.

The biomarker approach has also been used for prognostic purposes, by quantifying levels of metabolite(s) that predict severity of sepsis. *See* the '969 publication. The method involves measuring the age, mean arterial pressure, hematocrit, patient temperature, and the

concentration of one or more metabolites that are predictive of sepsis severity. Analysis of a blood sample from a patient with sepsis establishes the concentration of the metabolite, after which the severity of sepsis infection can be determined by analyzing the measured values in a weighted logistic regression equation. *See* the '969 publication.

A method based on determination of blood levels of antitrypsin (ATT) or fragments thereof, and transthyretin (TTR) or fragments thereof has been described for the diagnosis, prediction or risk stratifcation for mortality and/or disease outcome of a subject that has or is suspected to have sepsis. *See* the '631 publication. Presence and/or level of ATT or its fragments is correlated with increased risk of mortality and/or poor disease outcome if the level of ATT is *below* a certain cut-off value and/or the level of fragments thereof is *above* a certain cut-off value. Similarly, increased risk of mortality and/or poor disease outcome exist if the level of TTR is *below* a certain cut-off value and/or the level of its fragments is also *below* a certain cut-off value. *See* the '631 publication.

CLINICAL DATA ANALYTICS

The amount of data acquired electronically from patients undergoing intensive care has grown significantly during the past decade. Before it becomes knowledge for diagnostic and/or therapeutic purposes, bedside data must be extracted and organized to become information, and then an expert can interpret this information. Artificial intelligence applications in the intensive care unit represent an important use of such technologies. *See* Hanson et al. (2001). The use of computers to extract information from data and enhance analysis by the human clinical expert is a largely unrealized role for artificial intelligence. However, a variety of novel, computer-based analytic techniques have been developed recently. Although some of the earliest artificial intelligence applications were medically oriented, AI has not been widely accepted in medicine. Despite this, patient demographic, clinical, and billing data are increasingly available in an electronic format and therefore susceptible to analysis by intelligent software. The intensive care environment is therefore particularly suited to the implementation of AI tools because of the wealth of available data and the inherent opportunities for increased efficiency in inpatient care. A variety of new AI tools have become available in recent years that can function as intelligent assistants to clinicians, constantly monitoring electronic data streams for important trends, or adjusting the settings of bedside devices. The integration of these tools into the intensive care unit can be expected to reduce costs and improve patient outcomes. *See* Hanson et al. (2001).

Extensive efforts are being devoted to adding intelligence to medical devices, with various degrees of success. *See* Begley et al. (2000). Numerous technologies are currently used to create expert systems. Examples include: rule-based systems; statistical probability systems, Bayesian belief networks; neural networks; data mining; intelligent agents, multiple-agent systems; genetic algorithms; and fuzzy logic. Examples of specific uses include: pregnancy and child-care health information; pattern recognition in epidemiology, radiology, cancer diagnosis and myocardial infarction; discovery of patterns in treatments and outcomes in studies on epidemiology, toxicology and diagnosis; searches for and retrieval of relevant information from the internet or other knowledge repositories; and procedures that mimic evolution and natural selection to solve a problem.

In the modern healthcare system, rapidly expanding costs/complexity, the growing myriad of treatment options, and exploding information streams that often do not effectively reach the front lines hinder the ability to choose optimal treatment decisions over time. A general purpose (non-disease-specific) computational/artificial intelligence (AI) framework to address these challenges has been developed. *See* Bennett et al. (2013). This framework serves two potential functions, viz., a simulation environment for exploring various healthcare policies, payment methodologies, and providing the basis for clinical artificial intelligence. The approach combines Markov decision processes and dynamic decision networks to learn from clinical data and develop complex plans via simulation of alternative sequential decision paths while capturing the sometimes conflicting, sometimes synergistic interactions of various components in the healthcare system. It can operate in partially observable environments (in the case of missing observations or data) by maintaining belief states about patient health status and functions as an online agent that plans and re-plans as actions are performed and new observations are obtained.

Bennett and Hauser evaluated the framework using real patient data from an electronic health record, optimizing "clinical utility" in terms of cost-effectiveness of treatment (utilizing both outcomes and costs) and reflecting realistic clinical decision-making. The results of computational approaches were compared to existing treatment-as-usual (TAU) approaches, and the results demonstrate the feasibility of this approach. The AI framework easily outperformed the current TAU case-rate/fee-for-service models of healthcare. Using Markov decision processes, for instance, the cost per unit of outcome change (CPUC) was $189 vs. $497 for TAU (where lower CPUC is considered optimal) – while at the same time the AI approach could obtain a 30-35% increase in patient outcomes. According to Bennett and Hauser, modifying certain AI model parameters could further enhance this advantage, obtaining

approximately 50% more improvement (outcome change) for roughly half the costs. Thus, given careful design and problem formulation, an AI simulation framework can approximate optimal decisions even in complex and uncertain environments.

ARTIFICIAL INTELLIGENCE FOR SEPSIS DIAGNOSIS

Development and assessment of a data-driven method that infers the probability distribution of the current state of patients with sepsis, likely trajectories, optimal actions related to antibiotic administration, prediction of mortality and length-of-stay have been conducted. *See* Tsoukalas et al. (2015). A data-driven, probabilistic framework for clinical decision support in sepsis-related cases was constructed, first defining states, actions, observations and rewards based on clinical practice, expert knowledge and data representations in an EHR dataset of 1492 patients. Partially Observable Markov Decision Process (POMDP) model was used to derive the optimal policy based on individual patient trajectories and the performance of the model-derived policies was evaluated in a separate test set. Policy decisions were focused on the type of antibiotic combinations to administer. Multi-class and discriminative classifiers were used to predict mortality and length of stay. Data-derived antibiotic administration policies led to a favorable patient outcome in 49% of the cases, versus 37% when the alternative policies were followed (P=1.3e-13).

Sensitivity analysis on the model parameters and missing data argued for a highly robust decision support tool that withstands parameter variation and data uncertainty. When the optimal policy was followed, 387 patients (25.9%) had 90% of their transitions to better states and 503 patients (33.7%) patients had 90% of their transitions to worse states (P=4.0e-06), while in the non-policy cases, these numbers are 192 (12.9%) and 764 (51.2%) patients (P=4.6e-117), respectively. Furthermore, the percentage of transitions within a trajectory that led to a better or better/same state were significantly higher by following the policy than for non-policy cases (605 vs 344 patients, P=8.6e-25). Mortality was predicted with an AUC of 0.7 and 0.82 accuracy in the general case and similar performance was obtained for the inference of the length-of-stay (AUC of 0.69 to 0.73 with accuracies from 0.69 to 0.82). Thus, a data-driven model was able to suggest favorable actions, predict mortality and length of stay as above. *See* Tsoukalas et al. (2015).

For sepsis monitoring and control, a computer-implemented alerting method has been developed. *See* the '449 patent. The method involves automatically extracting with a computer system, from records maintained for a patient under care in a healthcare facility, information from an electronic medical record, and obtaining with the computer system information about

real-time status of the patient. The method also involves using the information from the electronic medical record and the information about the real-time status to determine whether the patient is likely to be suffering from dangerous probability of sepsis, using information from the electronic medical record to determine whether treatment for sepsis is already being provided to the patient, and electronically alerting a caregiver over a network if it is determined that a potentially dangerous level of sepsis exists and that treatment for sepsis is not already being provided. *See* the '449 patent.

The complexity of contemporary medical practice has impelled the development of different decision-support aids based on artificial intelligence and neural networks. Distributed associative memories are neural network models that fit well with the concept of cognition emerging from current neurosciences. A context-dependent autoassociative memory model has been reported, *see* Pomi et al. (2006), in which sets of diseases and symptoms are mapped onto bases of orthogonal vectors. A matrix memory stores associations between the signs and symptoms, and their corresponding diseases. In an implementation of the application with real data, a memory was trained with published data of neonates with suspected late-onset sepsis in a neonatal intensive care unit. A set of personal clinical observations was used as a test set to evaluate the capacity of the model to discriminate between septic and non-septic neonates on the basis of clinical and laboratory findings.

Results showed that matrix memory models with associations modulated by context could perform automated medical diagnoses. The sequential availability of new information over time makes the system progress in a narrowing process that reduces the range of diagnostic possibilities. At each step the system provides a probabilistic map of the different possible diagnoses to that moment. The system can incorporate the clinical experience, building in that way a representative database of historical data that captures geo-demographical differences between patient populations. The trained model succeeded in diagnosing late-onset sepsis within the test set of infants in the NICU: sensitivity 100%; specificity 80%; percentage of true positives 91%; percentage of true negatives 100%; accuracy (true positives plus true negatives over the totality of patients) 93,3%; and Cohen's kappa index 0,84.

An electronic sepsis surveillance system (ESSV) was developed to identify severe sepsis and determine its time of onset. ESSV sensitivity and specificity were evaluated during an 11-day prospective pilot study and a 30-day retrospective trial. *See* Brandt et al. (2015), ESSV diagnostic alerts were compared with care team diagnoses and with administrative records, using expert adjudication as the standard for comparison. ESSV was 100% sensitive for detecting severe sepsis but only 62.0% specific. During the pilot study, the software identified

477 patients, compared with 18 by adjudication. In the 30-day trial, adjudication identified 164 severe sepsis patients, whereas ESSV detected 996. ESSV was more sensitive but less specific than care team or administrative data. ESSV-identified time of severe sepsis onset was a median of 0 hours later than by adjudication (interquartile range = 0.05).

A retrospective, data-driven analysis, based on neural networks and rule-based systems has been applied to the data of two clinical studies of septic shock diagnosis. *See* Brause et al. (2001). The approach included steps of data mining, i.e., building up a database, cleaning and preprocessing the data and finally choosing an adequate analysis for the patient data. Two architectures based on supervised neural networks were chosen. Patient data was classified into two classes (survived and deceased) by a diagnosis based either on the black-box approach of a growing RBF network, and otherwise on a second network which could be used to explain its diagnosis by human understandable diagnostic rules. Advantages and drawbacks of these classification methods for an early warning system were identified.

It has been recommended that mortality risk stratification or severity-of-illness scoring systems be utilized in clinical trials and in practice to improve the precision of evaluation of new therapies for the treatment of sepsis, to monitor their utilization and to refine their indications. *See* Barriere et al. (1995). With the increasing influence of managed care on healthcare delivery, there will be increased demand for techniques to stratify patients for cost-effective allocation of care. Severity of illness scoring systems are widely utilized for patient stratification in the management of cancer and heart disease.

Mortality risk prediction in sepsis has evolved from identification of risk factors and simple counts of failing organs, to techniques that mathematically transform a raw score, comprised of physiologic and/or clinical data, into a predicted risk of death. Most of the developed systems are based on global ICU populations rather than upon sepsis patient databases. A few systems are derived from such databases. Mortality prediction has also been carried out from assessments of plasma concentrations of endotoxin or cytokine (IL-1, IL-6, TNF-α). While increased levels of these substances have been correlated with increased mortality, difficulties with bioassay and their sporadic appearance in the bloodstream prevent these measurements from being practically applied. The calibration of risk prediction methods comparing predicted with actual mortality across the breadth of risk for a population of patients is excellent, but overall accuracy in individual patient predictions is such that clinical judgment must remain a major part of decision-making. With databases of appropriate patient information increasing in size and complexity, clinical decision making requires the innovation of a reliable scoring system. *See* Angus et al. (2013).

Dynamic Bayesian Networks, a temporal probabilistic technique to model a system whose state changes over time, was used to detect the presence of sepsis soon after the patient visits the emergency department. *See* Nachimuthu et al. (2012). A model was built, trained and tested using data of 3,100 patients admitted to the emergency department, and the accuracy of detecting sepsis using data collected within the first 3 hours, 6 hours, 12 hours and 24 hours after admission was determined. The area under the curve was 0.911, 0.915, 0.937 and 0.944 respectively.

Application of new knowledge based methods to a septic shock patient database has been proposed, and an approach has been developed that uses wrapper methods (bottom-up tree search or ant feature selection) to reduce the number of properties. *See* Fialho et al. (2012). The goal was to estimate, as accurately as possible, the outcome (survived or deceased) of septic shock patients. A wrapper feature selection based on soft computing methods was applied to a publicly available ICU database. Fuzzy and neural models were derived and features were selected using a tree search method and ant feature selection.

An attempt has been made to support medical decision making using machine learning for early detection of late-onset neonatal sepsis from off-the-shelf medical data and electronic medical records (EMR). *See* Mani et al. (2014). Data used were from 299 infants admitted to the neonatal intensive care unit and evaluated for late-onset sepsis. Gold standard diagnostic labels (sepsis negative, culture positive sepsis, culture negative/clinical sepsis) were assigned based on all the laboratory, clinical and microbiology data available in EMR. Only data that were available up to 12 h after phlebotomy for blood culture testing were used to build predictive models using machine learning (ML) algorithms. Sensitivity, specificity, positive predictive value and negative predictive value of sepsis treatment of physicians were compared with predictions of models generated by ML algorithms.

Treatment sensitivity of all the nine ML algorithms and specificity of eight out of the nine ML algorithms tested exceeded that of the physician when culture-negative sepsis was included. When culture negative sepsis was excluded both sensitivity and specificity exceeded that of the physician for all the ML algorithms. The top three predictive variables were the hematocrit or packed cell volume, chorioamnionitis and respiratory rate. *See* Rangel-Fausto et al. (1995); and Mani et al. (2014).

The importance of preprocessing in clinical databases has been recognized. Specifically in intensive care units, data is often irregularly recorded, contain a large amount of missing values and sampling times are uneven. A systematic preprocessing procedure has been proposed, *see* Marques et al. (2011), that can be generalized to common clinical databases. This

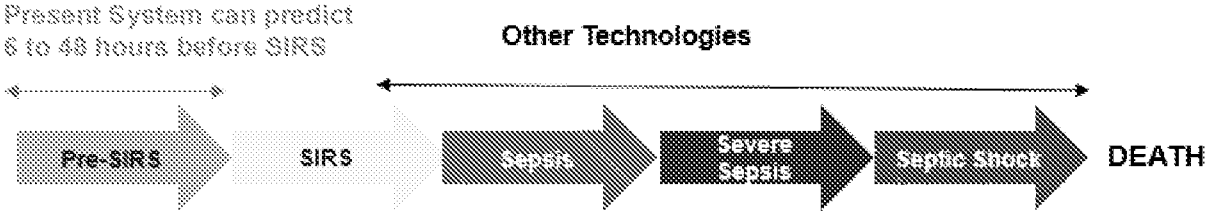
procedure was applied to a known septic shock patient database and classification results were compared with previous studies. The goal was to estimate, as accurately as possible, the outcome (survived or deceased) of these septic shock patients. Neural modeling was used for classification, and results showed that preprocessing improved classifier accuracy. *See* Marques et al. (2011).

SUMMARY OF THE INVENTION

The present invention relates to the composition and use of clinical parameters (or features) for the prediction or risk stratification for Systemic Inflammatory Response Syndrome (SIRS) several hours to days before SIRS symptoms are observable for a definitive diagnosis in a patient, and relates to the development of groups of parameters and corresponding prediction models for predicting onset of a disease, e.g., as SIRS. The ability to predict the onset of SIRS, prior to the appearance of clinical symptoms, enables physicians to initiate therapy in an expeditious manner, thereby improving outcomes. This applies to patients that have non-infectious SIRS or patients with SIRS that progress to sepsis. The ability to predict a disease, e.g., SIRS, is useful for healthcare professionals to provide early prophylactic treatment for hospitalized patients, who will otherwise develop sepsis and/or conditions – such as pancreatitis, trauma, or burns - that share symptoms identical or similar to, for example, SIRS.

Moreover, such a predictive ability can also be applied to enhance patient care during clinical trials. A clinical trial is a prospective biomedical or behavioral research studies on human subjects that is designed to answer specific questions about biomedical or behavioral interventions (novel vaccines, drugs, treatments, devices or new ways of using known interventions), generating safety and efficacy data. The patients can include patients who develop SIRS or SIRS-like symptoms when they are enrolled in clinical trials investigating a variety of pre-existing conditions. For example, a medical device company could be conducting a trial for an implantable device such as hip replacement system, or a pharmaceutical company could be conducting a trial for a new immunosuppressant for organ recipients. In both scenarios, the clinical trial protocol would concentrate on functional and recovery measurements. If trial investigators had access to a method that predicted which patients were infected during the operation, or at any time during the trial, they would be able to provide early treatment, and minimize adverse events and patient dropout. Correspondingly the same method can also be used to screen patients during the initial phase of patient enrollment: a potential enrollee predicted to develop SIRS could first be treated or excluded from the trial, thereby reducing adverse or confounding results during the trial.

The invention is based on combinatorial extraction and iterative prioritization of clinical parameters and measurements (or, collectively, "features") commonly available in healthcare settings in the form of common patient measurements, laboratory tests, medications taken, fluids and solids entering and leaving the patient by specified routes, to correlate their presence and temporal fluctuations to whether a patient would ultimately develop SIRS. This group of clinical parameter combinations has not been previously associated with SIRS or related to its progression and risk stratification. The invention relates, in general, to the identification and prioritization of these clinical parameters and measurements, or combinations thereof, for the prediction (or predictive modeling) of SIRS. As shown in the below timeline, the invention enables the prediction of SIRS well prior to a prediction time (and/or a time of diagnosis) enabled by existing technologies.



BRIEF DESCRIPTION OF FIGURES

Figure 1 illustrates an embodiment of the system utilized in the present disclosure.

DETAILED DESCRIPTION

This invention describes the identification of seemingly unrelated physiologic features and clinical procedures, combinations of which can be used to predict accurately the likelihood of a SIRS-negative patient becoming diagnosed as SIRS-positive 6 to 48 hours (e.g., 6, 12, 24 or 48 hours) later.

The MIMIC II database contains a variety of hospital data for four intensive care units (ICUs) from a single hospital, the Beth Israel Deaconess Medical Center (BIDMC) in Boston. MIMIC itself stands for "Multiparameter Intelligent Monitoring in Intensive Care," and this second version is an improvement on the original installment. The hospital data tabulated is time-stamped and contains physiological signals and measurements, vital signs, and a comprehensive set of clinical data representing such quantitative data as medications taken (amounts, times, and routes); laboratory tests, measurements, and outcomes; feeding and ventilation regimens; diagnostic assessments; and billing codes representing services received. MIMIC II contains information for over 33,000 patients collected between 2001 and 2008 from the medical ICU (MICU), surgical ICU (SICU), coronary care unit (CCU) and cardiac surgery

recovery unit (CSRU), as well as the neonatal ICU (NICU). Operationally MIMIC II is organized as a relational PostgreSQL database that can be queried using the SQL language, for convenience and flexibility. The database is organized according to individual patients, each denoted by a unique integer identification number. A particular patient may have experienced multiple hospital admissions and multiple ICU stays for each admission, which are all accounted for in the database. To comply with the Health Insurance Portability and Accountability Act (HIPAA), the individuals in the database were de-identified by removing protected health information (PHI). Moreover, the entire time course for each patient (e.g., birthday, all hospital admissions, and ICU stays) was time-shifted to a hypothetical period in the future, to further reduce the possibility of patient re-identification.

Data Preparation

Although the MIMIC II database was used as a source of measurements and other data for the invention, the invention disclosed here is not limited by the MIMIC II database or the specific measurements, representations, scales, or units from the BIDMC or the MIMIC II database. For example, the units that are used to measure a feature for use in the invention may vary according to the lab or location where the measurement occurs. The standard dose of medication or route of administration may vary between hospitals or hospital systems, or even the particular member of a class of similar medications that are prescribed for a given condition may vary. Mapping of the specific features found in the MIMIC II database to those used in another hospital system are incorporated into the invention disclosed here to make use of this invention in a different hospital. For example, if the MIMIC II database measures the weight of patients in pounds and another hospital does so in kilograms, one of ordinary skill in the art would appreciate that it is a simple matter to convert the patients' weights from kilograms to pounds. Likewise, it is straightforward to adjust the predictive formula of the invention to accept kilograms instead of pounds. This sort of mapping between features also can be done between medications that carry out the same functions, but may differ in standard dosages, and/or alternative laboratory measurements that measure the same parameter, vital sign or other aspect in a patient, etc.

In addition, rather than mapping feature-to-feature as described in the above paragraph and then using the exemplary models presented here with the newly mapped features, it is straightforward to use the methods of the invention taught here to take existing hospital datasets and retrain models in accordance with the techniques of the invention described herein. Those models can then be used predictively, in the manner of the invention shown here. The same

feature removal and feature selection methods can be used, or the features found useful here can guide hand-curated feature selection methods. All of this would be apparent to one of ordinary skill in the art.

The MIMIC II Database is available online at the following site [https://physionet.org/mimic2/], and is incorporated herein by reference in its entirety. As a person of ordinary skill in the art would appreciate, the MIMIC II database can be readily and easily accessed as follows. Information at the website https://physionet.org/mimic2/mimic2_access.shtml describes how to access the MIMIC II clinical database. First one needs to create a PhysioNetWorks account at https://physionet.org/pnw/login. One then follows the directions at https://physionet.org/works/MIMICIIClinicalDatabase/access.shtml, which includes completing a training program in protecting human research participants (which can be accomplished online) because of research rules governing human subjects data. Finally, one applies for access to the database by filling out an application, including certification from the human subjects training program and a signed data use agreement. These are common steps familiar to one of ordinary skill in the art when dealing with such medical data on human subjects and one of ordinary skill in the art would expect such steps to be taken. Approved applicants, such as a person of ordinary skill in the art, receive instructions by email for accessing the database. When updated (including the recent release of the MIMIC III database), the updated features can be used as described herein for prediction of SIRS, and are within the scope of the invention.

Data were obtained from the MIMIC II Database from the tables representing chart measurements, laboratory measurements, drugs, fluids, microbiology, and cumulative fluids for patients. *See* Saeed et al. (2011). The following tables were used to extract patient data used according to the invention for prediction:

(1) The chart events table contains charted data for all patients. We recorded the patient id, the item id, the time stamp, and numerical values.

(2) The lab events table contains laboratory data for all patients. We recorded the patient id, the item id, the time stamp, and numerical values.

(3) The io events table contains input and output (fluid transfer) events for all patients. We recorded the patient id, the item id, the time stamp, and numerical value (generally of the fluid volume).

(4) The micro events table contains microbiology data for all patients. We recorded the patient id, the item id, the time stamp, and the result interpretation. The result interpretation that we gather is based on 2 categories 'R' (resistant) and 'S' (sensitive) that are mapped to 1 and -1 values, respectively.

(5) The med events table contains medication data for all patients. We recorded the patient id, the item id, the time stamp, and the medication dose.

(6) The total balance (totalbal) events table contains the total balance of input and output events. We recorded the patient id, the item id, the time stamp, and the cumulative io volume.

As a person of ordinary skill in the art would appreciate, the above entries, those in Tables 1 to 7 herein, and those in the MIMIC II database correspond to features (as shown in the MIMIC II database and below) identified by well-known abbreviations that have well-known meanings to those of ordinary skill in the art. Moreover, the corresponding entries, such as measurements and other parameters, in the MICMI II database are features in accordance with the invention.

All patients with sufficient data in the MIMIC II database, except those that spent any time in the neonatal ICU, were included in the development. Patients who met at least two of the four conditions for SIRS simultaneously at some point in their stay were identified from the database. (The four conditions are a temperature of less than 36° C or greater than 38° C, a heart rate of greater than 90 beats per minute, a respiratory rate of greater than 20 breaths per minute, and a white blood cell (WBC) count of less than 4,000 per microliter or greater than 12,000 per microliter.) We checked for the occurrence of SIRS using all 6 possible 2-condition cases for each patient during their ICU stays without repetition at any given time using time-stamped chart times. The occurrence of SIRS is modeled as a point process which requires that the 2 or more SIRS conditions occur simultaneously. Heart rate was extracted from item id 211 in the chart events table. Respiration rate measurement was extracted by item ids 219, 615, and 618 in the chart events table. Temperatures were extracted from item ids 676, 677, 678, and 679 in the chart events table. Finally, WBC measurements were extracted from item ids 50316 and 50468 in the lab events table. Where multiple sources of a measurement were available, the one most recently updated at the time point was used.

Each time SIRS conditions occurred in a patient, we recorded the time stamped date and time of the SIRS occurrence and the patient id. We used the timestamps of positive patients to

collect data from the 7 tables as described above 6, 12, 24, and 48 hours (the "time point") before the occurrence of SIRS, using the most recent data nearest the time point for each patient, but no later than 1 week before the onset or any time before the current stay. For all patients for which no SIRS occurrence was found (SIRS negative patients), we recorded their ids. Using their ids, we collected data for 6, 12, 24 and 48 hours before some point in their last recorded stay. The ids for positive patients and negative patients are disjoint sets. The numbers of positive, negative, and total patients for the 48-hour time point was 9,029, 5,249, and 14,278, respectively; for the 24-hour time point 11,024, 5,249, and 16,273; for the 12-hour time point 13,033, 5,249, and 18,282; and for the 6-hour time point 15,075, 5,249, and 20,324. These numbers are different at different time points (and grow for shorter times) because fewer patients were present in the ICU 48 hours before the onset of SIRS than were present 6 hours before the onset of SIRS.

Data were normalized to a mean of zero and standard deviation of one. That is, a normalized version of each datum was created by subtracting the mean for each feature (taken across all occurrences for each feature or measurement type) and divided by the standard deviation (taken across the same distribution). The distribution of each feature property in the data was compared between the positives (patients who met the criteria for SIRS) and negatives (those that did not) at each of the four time points using the Bhattacharyya distance. That is, a histogram giving the population of SIRS-positive patients as a function of the measured value of some feature was compared to the same histogram but for SIRS-negative patients, and the Bhattacharyya distance was computed between these two histogram distributions. Any feature whose Bhattacharyya distance was less than 0.01 at all four time points was removed from further consideration. *See* Bhattacharyya (1943). The list of features after this step and used in the next steps of the analysis, as well as the mean and standard deviation of each feature, is shown in **Table 1**.

Table 1. The list of features extracted from the MIMIC II database after the Bhattacharyya procedure described in the text is given in the first column (using the MIMIC II identifiers or IDs), the mean for each feature across the patient measurements used in this study are given in the second column, and the standard deviation for each feature across the same distribution of patient measurements is given in the third column.

Feature ID	Mean	Standard Deviation
chart 2	0.00085647	0.02855790
chart 4	0.09469113	3.17506964
chart 5	0.09931363	3.34506569
chart 25	0.36479470	7.86772704
chart 26	0.52791918	12.94497598

Feature ID	Mean	Standard Deviation
chart 29	-0.05025127	1.71765410
chart 63	0.01411262	0.44388419
chart 65	0.25089882	11.57072921
chart 79	0.12028499	3.70876085
chart 92	0.30364889	4.83353618
chart 142	-0.01564594	3.97578730
chart 146	0.60699444	20.67946954
chart 181	0.22106800	5.34978160
chart 186	0.58731250	5.66550401
chart 192	0.15565999	4.92768741
chart 221	0.04279908	0.53402450
chart 226	0.05647857	1.15417713
chart 440	0.02739493	0.39652687
chart 441	0.00281059	0.10200107
chart 442	0.89347991	10.75176971
chart 449	0.13689356	1.32076222
chart 472	15.32213520	114.07135964
chart 473	7.60184896	55.95736185
chart 481	0.27143391	4.52794496
chart 482	0.24527245	5.40135244
chart 483	0.16893122	3.74289763
chart 484	0.43437456	7.34509454
chart 485	0.23984452	4.16349239
chart 490	1.00636153	20.52072585
chart 491	0.62665725	4.21715369
chart 492	1.82722530	8.25509216
chart 494	0.00080165	0.03223063
chart 496	0.01173124	0.43029790
chart 498	0.10166860	0.81219774
chart 503	0.01031891	0.62436918
chart 512	0.96757982	16.61775297
chart 517	2.84696589	13.68963861
chart 595	1.66920135	10.23611224
chart 601	0.41964772	4.03303813
chart 602	0.20118514	1.91755499
chart 607	0.01587524	0.86210144
chart 624	0.09279608	2.99007718
chart 626	42.64198104	215.05044423
chart 664	1.15885278	9.03981262
chart 670	0.02115207	0.76604451
chart 671	0.00072793	0.02546059
chart 682	63.59648566	189.80611025
chart 683	62.40508426	186.76148116
chart 686	0.01310848	0.34099410
chart 725	0.00427231	0.23324051
chart 727	0.01532077	0.85030301
chart 773	13.59515581	58.13663911

Feature ID	Mean	Standard Deviation
chart 779	26.86192608	68.96123873
chart 781	9.25061379	16.73587842
chart 784	84.80022284	458.89082645
chart 785	5.12691634	31.66196336
chart 789	7.21857636	35.08988939
chart 792	0.27696501	8.44017613
chart 793	15.37957230	265.41501495
chart 807	27.76192457	59.15571578
chart 809	0.00328444	0.09765775
chart 811	53.96478158	72.76417086
chart 815	0.44755771	0.89990497
chart 817	29.91306924	253.35321509
chart 818	0.23468293	1.49861009
chart 821	0.74681259	1.04674692
chart 826	0.01572763	0.70942705
chart 828	83.80563920	118.11615467
chart 835	0.21953355	3.85647957
chart 836	4.99966513	38.32880772
chart 844	0.02802563	1.51344740
chart 850	6.46337022	36.52996134
chart 851	0.10410908	1.51648228
chart 856	0.03264113	0.81953706
chart 1162	7.12888622	15.20614694
chart 1223	0.00487930	0.29281632
chart 1340	0.00917443	0.37187792
chart 1390	13.26147798	105.84980386
chart 1391	8.10418715	58.66008183
chart 1397	1.60976889	9.98859281
chart 1401	13.30554577	105.97517485
chart 1402	6.59470944	52.04974798
chart 1411	0.03272241	1.05123619
chart 1486	0.01720523	0.66680868
chart 1520	2.30231283	19.78048269
chart 1524	5.55297194	30.98367694
chart 1526	15.37957230	265.41501495
chart 1528	12.79354842	69.03612583
chart 1529	41.13133466	67.21985389
chart 1531	0.20717948	1.46503589
chart 1532	0.58986881	0.99893334
chart 1537	0.02334010	1.40616562
chart 1540	5.08306486	33.01429097
chart 1546	0.01264883	0.42526786
chart 1565	0.00798070	0.37051630
chart 1624	0.16967560	3.58526348
chart 1671	0.04965681	2.65454906
chart 2139	0.07565662	3.23055891
chart 5683	0.09686892	4.15236669

Feature ID	Mean	Standard Deviation
chart 5816	0.00266038	0.11524787
chart 5818	0.14924620	2.05413428
chart 6702	0.24175311	4.39982998
chart 6711	0.00245132	0.14175629
chart 6712	0.00294159	0.15337553
lab 50001	23.22076458	100.41719985
lab 50013	7.69303340	22.24716472
lab 50017	0.32463216	2.03215748
lab 50019	50.42589412	87.47914829
lab 50030	0.24833007	0.49748206
lab 50038	5.03150301	377.69248727
lab 50042	0.01275856	0.54636087
lab 50044	6.24396591	567.17187703
lab 50055	0.05298472	1.03827871
lab 50056	0.15714736	3.52138287
lab 50059	297.50420651	13326.87658960
lab 50061	70.64888293	113.60306928
lab 50062	31.87699226	170.59063119
lab 50064	1.24808645	10.19100689
lab 50071	0.12456226	8.81696541
lab 50072	0.02155964	0.55970162
lab 50073	36.01986023	200.55947412
lab 50075	1.21495658	12.11099863
lab 50076	0.29621912	3.03200984
lab 50077	6.36559620	241.37014245
lab 50078	1.23008325	72.98495642
lab 50082	1.74522064	51.65243614
lab 50086	117.89271088	464.52399231
lab 50087	5.49516077	25.82523777
lab 50089	1.00971800	6.69502589
lab 50093	1.97097081	27.92531610
lab 50094	0.12298641	5.70363476
lab 50098	0.05717421	3.36660155
lab 50099	4.61501799	34.14694339
lab 50101	50.01726542	193.59327847
lab 50102	0.06362372	1.10232089
lab 50106	0.13661110	3.26226671
lab 50107	0.45142877	16.02191354
lab 50109	6.10556506	69.46251026
lab 50115	12.86690919	57.08667334
lab 50120	20.83012709	1090.70498689
lab 50129	7.27576402	89.66349837
lab 50130	37.76052003	280.74132309
lab 50138	17.53646157	131.58751595
lab 50144	15.88692719	66.47903839
lab 50146	0.04576709	1.07028846
lab 50152	0.88600778	69.38537896

Feature ID	Mean	Standard Deviation
lab 50154	5.49521705	49.55527991
lab 50158	0.20605360	4.50194703
lab 50164	0.02401253	0.44999333
lab 50165	2.36349512	34.51166865
lab 50167	2.17450584	231.32404185
lab 50173	31.31925548	77.23835655
lab 50179	0.39315773	5.09912488
lab 50181	94.34078891	272.00067686
lab 50190	40.72391222	100.42871234
lab 50195	307.93628798	2596.86410786
lab 50196	0.01733043	0.39757285
lab 50202	0.20942270	5.09167981
lab 50204	2.09826473	37.28375222
lab 50208	0.07031797	2.95357221
lab 50212	32.28998809	1822.22575476
lab 50216	0.01408811	0.74006392
lab 50217	0.27062614	5.69846437
lab 50218	1.92383387	77.28189759
lab 50225	0.00780922	0.76859856
lab 50226	0.04006163	2.41405113
lab 50232	0.04272307	3.01560050
lab 50235	0.14869029	3.05652875
lab 50237	0.09455106	2.75161652
lab 50239	0.00166690	0.05087849
lab 50240	1.51154457	14.25533386
lab 50241	9.39977588	352.74628108
lab 50247	0.09132932	5.45906917
lab 50250	0.13962040	6.88993531
lab 50251	0.01882266	0.97346587
lab 50252	0.06709623	2.62018469
lab 50253	0.13093571	5.12523144
lab 50254	7.03257581	97.77120331
lab 50255	4.68506799	173.98288638
lab 50258	0.10672830	2.78573420
lab 50259	4.74681328	155.39408808
lab 50260	11.65093150	1385.01063408
lab 50261	4.34458608	361.75381215
lab 50263	1.98564808	13.44359622
lab 50265	0.10524350	3.01526596
lab 50266	0.05532988	6.45357037
lab 50273	0.28632336	4.39336506
lab 50276	0.08971186	1.67879510
lab 50277	7.90530293	24.59478854
lab 50278	6.32139909	74.56982431
lab 50279	0.01213055	0.55230286
lab 50284	0.07129500	1.75647837
lab 50285	23.11024163	265.93045864

Feature ID	Mean	Standard Deviation
lab 50287	9.76370056	179.33304781
lab 50288	0.61341189	9.78191108
lab 50302	0.00545595	0.25048838
lab 50304	0.33916680	3.88564769
lab 50313	191.71262224	7100.57705838
lab 50314	45.76779934	2198.66177537
lab 50317	10.82248262	127.26177844
lab 50318	4.19766095	54.87326127
lab 50319	7.08626305	87.10633523
lab 50320	18.03138369	190.04396439
lab 50322	0.05020661	1.35116710
lab 50323	0.06843045	1.76870860
lab 50330	0.38097072	6.10177124
lab 50335	0.14723227	2.86477532
lab 50356	0.30287054	3.16345475
lab 50357	0.01400486	0.57214803
lab 50367	0.51411003	5.28545582
lab 50374	0.85250035	28.14780910
lab 50378	44.27892180	127.19341944
lab 50382	276.98644508	1654.09627098
lab 50385	0.00039817	0.02110789
lab 50390	0.00601975	0.34739895
lab 50395	0.00910492	0.46236088
lab 50404	0.12722370	5.45882054
lab 50427	0.00478592	0.26923167
lab 50428	231.69180006	112.32668925
lab 50434	0.02742736	0.73329938
lab 50436	0.47300042	7.79233392
lab 50437	0.07886259	2.88194189
lab 50438	0.12774898	3.39834450
lab 50441	0.02315450	0.49641135
lab 50451	3.21353796	14.71240938
lab 50460	0.29951090	5.80080856
lab 50461	0.04622496	2.05194982
lab 50463	0.64392486	11.17676477
lab 50465	0.13695896	4.38723417
lab 50466	0.21007844	7.29724834
lab 50469	0.02087127	1.31441149
lab 50473	0.00754074	0.48035113
lab 50510	0.00241630	0.13329013
lab 50511	0.00172760	0.10773917
lab 50513	0.00855629	0.47020900
lab 50526	56.17471342	1721.05586913
lab 50530	0.00098053	0.05020359
lab 50537	0.06201849	1.59872762
lab 50541	0.06614488	1.51504583
lab 50545	0.34937783	5.41626284

Feature ID	Mean	Standard Deviation
lab 50546	300.30688238	18625.78104190
lab 50548	127.38286758	3309.11019170
lab 50549	0.00105057	0.05486823
lab 50550	0.00322174	0.26541980
lab 50551	0.00119064	0.08156087
lab 50560	0.01072839	0.41973561
lab 50565	0.06933131	2.32126071
lab 50567	1.21979911	81.36029950
lab 50579	0.01884017	0.65461564
lab 50587	0.20333847	3.18805892
lab 50588	0.15634076	2.88158136
lab 50589	0.02133352	0.77524117
lab 50598	311.52946958	24113.47723120
lab 50599	18.46205351	1326.02925765
lab 50600	0.00266144	0.16482594
lab 50603	0.03637297	1.22923047
lab 50604	0.00632091	0.24963091
lab 50609	0.14016552	1.90214299
lab 50614	0.36558692	4.41471535
lab 50616	298.68821497	6959.19944596
lab 50617	35.65359878	1333.62922289
lab 50632	0.00077042	0.04183721
lab 50641	35.64576586	158.00230185
lab 50647	3.57980310	17.36721303
lab 50652	0.00539291	0.25281504
lab 50655	15.82295535	61.95048456
lab 50659	0.11790867	13.25911071
lab 50664	0.01456787	0.50219925
lab 50675	0.00616333	0.48115179
lab 50687	0.01151422	0.69778365
lab 50689	0.00814890	0.56889197
lab 50690	0.00042618	0.02947423
lab 50699	0.10274260	1.25007695
io 48	1.73658776	44.28782162
io 49	2.71781762	66.99138798
io 51	0.34689732	13.08254103
io 52	10.17957697	142.29269898
io 53	1.69344446	67.30777999
io 55	949.40834150	2722.10335736
io 58	0.90888080	27.62156522
io 59	6.91924639	60.88424044
io 60	54.64588878	302.96267120
io 61	22.99544754	204.39111258
io 63	0.97247514	62.50643457
io 64	26.86115002	397.70183709
io 65	34.37260120	222.61955003
io 66	1.19775179	72.37468407

Feature ID	Mean	Standard Deviation
io 68	0.33267965	19.37697438
io 70	0.75885978	22.67961529
io 71	4.37424709	79.19413878
io 72	1.20759210	49.73564850
io 73	0.42639025	17.85125962
io 74	0.36104496	12.30809779
io 76	28.97170472	179.26026786
io 77	0.54279311	21.93176386
io 80	0.35992436	29.88552815
io 84	0.18721109	10.40747286
io 85	0.47275529	19.61861269
io 87	0.48010926	30.50209458
io 88	0.24324135	9.76926775
io 91	0.73833870	25.44325971
io 92	0.04706542	2.97974170
io 93	0.37785404	21.59698881
io 94	42.35425130	388.86403879
io 97	0.52794509	31.04533368
io 102	279.29773078	753.16871790
io 104	195.77040202	638.74932511
io 106	153.23973362	693.60841995
io 107	14.33074544	207.92960485
io 123	24.94261801	292.21717716
io 124	208.90881076	954.80094392
io 125	20.33225942	315.34376435
io 128	1.44256899	39.17880469
io 130	56.51977168	357.54608426
io 131	28.55636877	277.83545815
io 132	6.35137975	43.61830338
io 133	8.38249132	74.27164202
io 134	320.54597983	1127.87536431
io 137	10.25941527	71.50864647
io 138	0.04529696	2.90709517
io 139	2.74161764	40.66924563
io 140	3.69234248	66.42834639
io 141	14.57634223	125.26022645
io 142	14.53412826	215.49989625
io 143	0.93220339	32.06141061
io 144	61.25270229	296.11008219
io 147	1.08450232	28.60256873
io 149	0.93797075	20.55435165
io 151	60.70526334	366.57431000
io 152	30.57171289	275.77108826
io 154	11.13338003	161.83482830
io 155	11.39340244	121.46558083
io 158	8.13713405	165.85419264
io 159	1.93360415	74.70328057

Feature ID	Mean	Standard Deviation
io 161	0.08140671	6.11974469
io 162	0.40646449	23.70814384
io 163	19.72272027	170.44853472
io 165	15.83192674	198.35616243
io 168	24.77472802	176.36505289
io 172	13.38121586	201.90597211
io 173	0.46374376	14.48458213
io 174	2.13662149	33.42709641
io 178	5.01133479	61.83270044
io 179	5.85099454	71.52839628
io 180	2.74793739	70.18325037
io 182	2.29146239	80.88997339
io 183	0.37544474	30.64093653
io 186	4.37953149	139.27499665
io 187	7.60228850	81.68098458
io 191	1.55195055	49.81525772
io 192	0.11136013	6.22326436
io 202	0.72655233	20.43935318
io 211	2.71494549	24.11026016
io 212	0.75392961	13.07604289
io 213	1.12146690	29.22385647
io 214	1.28388080	46.99541429
io 215	1.22984757	30.24580767
io 218	7.38712290	72.05692274
io 219	2.85509175	82.29106504
io 222	3.05610029	151.66292867
io 224	2.42779101	48.65060565
io 225	1.57627189	39.92990640
io 232	1.99257599	42.78019475
io 241	0.05518481	4.32167118
io 246	4.09721249	56.06843583
io 249	2.25915511	40.54325768
io 250	0.05503556	3.68110831
io 256	0.72516558	27.51467487
io 258	0.79983191	20.26407797
io 264	0.76265583	20.91930047
io 272	0.35362097	22.83911537
io 274	2.21739739	66.72062792
io 276	0.16598963	11.62852022
io 286	16.35137975	372.92534743
io 294	0.62522811	22.62024958
io 297	9.92812369	165.34368819
io 299	0.84535649	32.33607148
io 309	0.14876733	7.72623402
io 319	0.55427931	13.79992162
io 331	0.02521362	2.03521531
io 336	1.15142177	51.99660482

Feature ID	Mean	Standard Deviation
io 346	0.37085026	17.65801997
io 353	0.43987545	13.44523405
io 362	3.47473386	66.22076443
io 367	2.70948312	95.55443337
io 370	1.28904608	62.02432101
io 372	0.23394400	10.66215486
io 375	1.96216241	38.09575102
io 388	0.24513237	13.13709014
io 393	1.35958993	31.38702890
io 397	0.46400056	22.54992593
io 398	1.19107485	37.87508913
io 406	0.20310968	18.16141186
io 411	0.07567586	4.21071036
io 414	0.32353971	14.14960725
io 415	0.22762292	13.42311488
io 436	0.33718833	26.49641673
io 454	0.11939764	4.58772626
io 473	4.31411962	176.19192715
io 474	0.13252907	10.94617428
io 477	0.34700238	16.02948289
io 481	5.82171873	180.48098711
io 491	0.25213615	11.31837615
io 496	0.34278265	14.85375749
io 518	0.73819863	30.68261071
io 537	0.29415885	9.56261768
io 541	0.38709204	23.46093078
io 555	0.25756408	19.97592587
io 563	2.98907819	133.68862961
io 580	0.88948032	28.94821707
io 591	7.79520941	488.69346735
io 615	1.40565906	63.71466453
io 648	0.07984312	5.43627512
io 659	0.18679087	11.14743115
io 703	0.81881216	47.93904756
io 715	1.98718308	106.67294807
io 761	0.44081733	19.61930125
io 781	0.38380726	24.10652565
io 898	1.05757109	63.36826128
io 900	1.10827030	32.44354405
io 926	3.21893823	86.65195228
io 1101	0.25213615	15.51705456
io 1683	3.73966942	163.04782953
io 1698	0.03992156	3.08545750
io 1707	0.81923239	23.84415661
io 1867	0.20755708	9.68891084
io 1883	0.69227339	25.56599050
io 1898	0.32028295	14.07166623

Feature ID	Mean	Standard Deviation
io 3680	2.17134753	97.91951352
io 3692	0.67297092	23.45302190
io 4691	0.16759613	10.00683424
io 4692	0.03291602	2.16073240
med 25	46.81337278	216.13348495
med 47	0.00158135	0.12283066
med 49	0.41836614	7.36927477
med 115	0.00433139	0.20011319
med 118	0.63889367	9.07459691
med 120	0.00212875	0.05821205
med 123	0.02503612	0.55712674
med 126	0.05372515	1.14193471
med 127	0.03595630	1.75111724
med 133	0.24830962	3.46886288
med 134	0.00405895	0.19650777
med 163	0.00136277	0.10707113
totalbal 1	814.25867763	1516.14917639
totalbal 2	598.30432761	1021.08972972
totalbal 3	55.96514866	246.98815463
totalbal 4	0.48738546	9.22563007
totalbal 5	15.11870912	81.97208961
totalbal 6	5.11092240	54.36397034
totalbal 7	5.82342626	91.33320416
totalbal 8	1.43187293	28.48242708
totalbal 9	0.25374235	6.66952028
totalbal 10	0.04412383	3.07006251
totalbal 16	13.57840095	79.02372621
totalbal 18	441.86617120	815.10281506
totalbal 19	1.77952589	37.89367554
totalbal 20	140.43823982	296.05436437
totalbal 23	18.36761510	62.36754817
totalbal 24	4.99583432	58.63717272
totalbal 25	8.33850329	151.97044567
totalbal 26	488.44715335	820.26058063
totalbal 27	219.09744385	953.56024176
totalbal 28	434.20308217	1767.96178280

Machine Learning on Data

Machine learning was carried out with the scikit.learn package under Python language version 2.7 running in the Windows operating system within the environment Anaconda. In addition, we used the statistical software package R 3.1.2 (64-bit version) under Windows to perform tasks in data preparation and analysis. This scikit.learn package version 0.16.0 is designed to produce machine learning models for the purpose of classification and regression on dense and sparse datasets. The following classifiers were used: Nearest Neighbors, Linear

SVM (support vector machine), RBF SVM (radial basis function support vector machine), Decision Trees, Random Forest (RF), AdaBoost, Naive Bayes, and Logistic Regression (LR). The best classifier can be selected through model and parametric optimization. For some applications the best classifier might be that with the highest accuracy among all the classifiers tested. For other applications the best classifier might be the one with the highest positive predictive value (PPV), negative predictive value (NPV), specificity, selectivity, area under the curve (AUC), as defined below, or some other combination of performance attributes. For the examples presented here, accuracy was generally used to rate classifiers. Because the Logistic Regression performed very well, the machine learning results presented here use it unless otherwise stated. Although the foregoing is what we used for our work, a person of ordinary skill in the art would readily appreciate that many other machine learning concepts and algorithms could equally be used and applied in the methods of the invention, including but not limited to artificial neural networks (ANN), Bayesian statistics, case-based reasoning, Gaussian process regression, inductive logic programming, learning automata, learning vector quantization, informal fuzzy networks, conditional random fields, genetic algorithms (GA), Information Theory, support vector machine (SVM), Averaged One-Dependence Estimators (AODE), Group method of data handling (GMDH), instance-based learning, lazy learning, and Maximum Information Spanning Trees (MIST). Moreover, various forms of boosting can be applied with combinations of methods.

Some of these learning methods require additional parameters to run. For the complexity parameter in SVM and LR in separate runs we used values ranging from 0.0001 to 1000 by powers of ten. The same set of values were also applied to the gamma parameter in RBF SVM. The Decision Tree method was used with a maximum depth of 10, Adaboost had a minimum number of estimators equal to 50, and RF had a minimum of 50 estimators.

In a typical machine learning calculation set, and as we used here, independent of which classifier was being used, the original dataset was split in a random fashion into 2 datasets: a training dataset and a testing dataset, with the training dataset containing a random 80% of the data instances (an individual patient acquiring SIRS at a specific time [positive] or not [negative]) and the testing dataset containing the remaining 20% of the data. This separation of training from testing data is typical in supervised machine learning applications, so that the model developed in the training phase can be evaluated in the testing phase on data to which it has not previously been exposed (e.g., the testing data is equivalent to patients to whom the model has no exposure initially, but the model will make predictions about those patients after

exposure to the training data, and then those predictions can be evaluated by comparing them to the testing data itself that represents those patients).

For each of these classifiers, the model parameters that determine their predictive model were computed on the basis of the training dataset. For the logistic regression results reported here, the parameters for each resulting model are one coefficient for each data feature in the model plus a single bias value. A data feature is a type of measurement (systolic blood pressure measurement, for example). As shown in the equation below, a linear combination of coefficients (w_j) and normalized data features ($patient\_data_{i,j}$), together with the bias (b) produces the prediction.

Each classifier model was then used, with its own respective set of parameters obtained from the training dataset (as described above), and was evaluated on the testing dataset and prediction results were expressed in the form of accuracy, positive predictive value (PPV), sensitivity, specificity, negative predictive value (NPV), and area under the curve (AUC), as defined below.

The logistic regression was selected for its excellent accuracy, positive predictive value and its robustness. *See* Yu et al. (2011). Several random combinations of training and test datasets were used to reproduce the results. This strategy was used to eliminate the possibility that results were due to a serendipitous selection of the test dataset. The logistic regression model results presented here were run with complexity parameter set equal to 0.005 and penalty L2.

Predictions are made from the logistic regression model using the following equation:

$$P(SIRS|\text{patient\_data}_i) = \frac{1}{1 + \exp\left(-b - \sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$$

where $P(SIRS|\text{patient\_data}_i)$ is the probability that a particular patient i presenting normalized patient data represented by the vector patient_data_i will develop SIRS at the corresponding time point in the model, given the model bias parameter b and model coefficients w_j corresponding to the normalized patient feature measurements (of which there are num_features, indexed by j) $\text{patient\_data}_{i,j}$.

In the work presented here a probability of greater than 50% (one-half) results in a prediction of the patient having SIRS at the corresponding future time point, and a probability less than or equal to 50% (one-half) is a prediction of not having SIRS. As one of ordinary skill in the art would appreciate, it is straightforward to apply more sophisticated treatments of this

probability to assign finer grained priorities to the possibility and severity of a condition. For example, one could use the probability directly as a measure of the predicted probability of developing SIRS, where, rather than a binary prediction of which patients will or will not develop SIRS, one could map the probabilities to categories such as "highly likely to develop SIRS," "probably will develop SIRS," "could develop SIRS," "unlikely to develop SIRS," and "highly unlikely to develop SIRS." These finer grained priorities may be especially useful to hospitals in taking action on the predictions.

Feature Selection

A machine learning algorithm can be used to generate a prediction model based on a patient population dataset. However, there is a tremendous amount of data in the patient population dataset, much of which is not necessary or provides little contribution to the predictability of a particular disease for which the prediction model is being trained. Additionally, it is often the case that different particular patients only have available data for different respective subsets of all of the features of the datasets, so that a prediction model based on all of the features of the patient population dataset might not be usable for particular patients or might output suboptimal predictions for the particular patients. An example embodiment of the present invention identifies a plurality of subsets of features within the totality of features of the patient population dataset for which to produce respective prediction models, that can be used to predict a disease, e.g., SIRS, based on data of only the respective subset of features.

Thus, in an example embodiment of the present invention, a computer system is provided with a patient population dataset, from which the system selects a plurality of subsets, each subset being used by a machine learning algorithm, which is applied by the system to the respective subset, to train a new prediction model on the basis of which to predict for a patient onset of a disease, e.g., SIRS. Thus, for each selected subset, a respective prediction model can be trained, with each of the trained prediction models being subsequently applied to an individual patient's data with respect to the particular group of features of the subset for which the respective prediction model had been trained.

Thus, according to the example embodiment, in a preliminary selection step, a feature selection method is applied to select relevant subsets of features for training respective prediction models. In an example embodiment, prior to application of the feature selection method (or, viewed differently, as a first step of the feature selection method), features are initially removed from the dataset based on Bhattacharyya distance as described above. Then,

from those features not removed based on the Bhattacharyya distance, the system proceeds to select groups of relevant features to which to apply a machine learning algorithm, where the machine learning algorithm would then generate a respective prediction model based on data values of the selected relevant features of each of one or more of the groups.

The feature selection method includes computing the correlation between each feature at a given time point and the output array (–1 for negatives [patients who had not developed SIRS]; +1 for positives [patients who had developed SIRS at the target time]), and computing the correlation between all pairs of features at a given time point. Iteratively, a feature was selected as a primary feature at a time point if it had the greatest correlation with the output array amongst all of the remaining features for that time point (6, 12, 24, or 48 hours). Then, for that time point, all others of the remaining features that had a correlation of 60% or greater (when taken across patients) with the most recently selected primary feature at that time point (i.e., the primary feature selected for the present iteration) were selected as a secondary feature associated with that primary feature and time point. For example, in an example embodiment, for each feature, a vector is generated populated with a value for the respective feature for each of a plurality of patients of a patient population, and correlation is determined between the vector of the selected primary feature and the remaining feature vectors. The vectors can further be indicated to be associated with negatives or with positives.

All secondary features thus selected were then removed from the set of remaining features (so that once a feature is selected as a primary or secondary feature, it can no longer be selected as a primary feature in a subsequent iteration). This selected primary feature and its associated secondary features were together considered a feature group. Because of the method used to select a feature group, the members of a particular feature group had some correlation with the output (whether patients developed SIRS at a specific time in the future) and some correlation amongst themselves. Thus, they are expected to be useful in the prediction of SIRS, but members within a feature group might be partially redundant owing to their correlation amongst themselves. This process was repeated iteratively, first picking an additional primary feature at the same time point and then its associated secondary features at that time point (which together produced an additional feature group).

In an example embodiment, the iterative feature selection method is discontinued as soon as it is determined that the remaining unselected features have essentially no predictive power, as indicated by machine learning, e.g., with an AUC very close to 0.50 (such as 0.50 ± 0.05). For example, the system selects a primary feature and its secondary features as a new feature subset. The system then applies machine learning to the combination of all of the

remaining features of the patient population dataset. If the machine learning produces an operable prediction model based on those remaining features, then the system continues on with another iteration to find one or more further subsets of those remaining features that can be used alone. On the other hand, if the machine learning does not produce an operable prediction model based on those remaining features, then the iterative selection method is ended. Once the iterative selection method is ended, the system applies a machine learning algorithm to each of one or more, e.g., each of all, of the individual feature subsets that had been selected by the iterative feature selection method to produce respective prediction models.

In an example embodiment, this process is carried out separately for each of a plurality of values of a particular constraint, e.g., time points. For example, in an example, this method was performed for each of the noted four onset time points of 6, 12, 24, and 48 hours.

As one of ordinary skill in the art would readily appreciate, the above Machine Learning on Data and Feature Selection methods were carried out using the MIMIC II database, but the same methods of the invention could be utilized on another database from other hospitals to achieve the results of the invention, including identification of primary, secondary and additional features, exemplified here with the MICMI II database.

The feature selection method was applied to the entire patient population dataset. Once the relevant features were selected in this manner, the patient population dataset was divided into the training dataset and the testing dataset for performing the training and testing steps.

Example 1: Machine Learning Results Show Predictive Value of Selected Features

The performance results for machine learning with the linear support vector machine method (with the complexity parameter C=0.001) using data associated with the features in **Table 4** are shown in **Table 2**. Results for four separate sets of calculations are presented in this **Table 2**, each set corresponding to a respective onset time period. For each of the respective onset time periods, the table shows results of a calculation generated based on features grouped as primary and secondary features in the center column and results of calculations generated based on "remaining features" that were not removed in the Bhattacharyya procedure. The results show that the former calculations are predictive and the latter calculations are not predictive. **Table 3** shows further details of this "remaining features" set for the 48-hour dataset. Each calculation used a different set of data (collected 6, 12, 24, or 48 hours in advanced of the onset of SIRS for the positive patients). For each of the four sets of calculations, the results show that using only the data associated with the features in **Table 4**, accurate predictions could be made regarding which patients would and which would not

develop SIRS, as judged by statistical measures familiar to the machine learning community and a person of ordinary skill in the art, such as accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). In addition, the true positive rate (TP), true negative rate (TN), false positive rate (FP), and false negative rate (FN) are given. Parallel experiments using only feature data that were associated with features not primary or secondary for the associated time points dataset and not removed by the Bhattacharyya procedure ("remaining features") were unable to make accurate predictions regarding which patients would and which would not develop SIRS at the selected time, demonstrating the effectiveness of the invention. This is indicated by an area under the curve of very close to 50% when the remaining features were used.

The meanings for various terms in **Table 2** (and also used elsewhere in this application) are standard in the machine learning literature and are well known to one of ordinary skill in the art, but are referenced here in exemplary form for the sake of completeness. True positives (TP) are patients, whether in the training set or testing set, and whether historical or prospective, who are predicted to develop SIRS (generally in a given time window) and who do subsequently develop SIRS (generally in that given time window). True negatives (TN) are patients predicted not to develop SIRS who do not subsequently develop SIRS. False positives (TP) are patients predicted to develop SIRS but who do not subsequently develop SIRS, and false negatives (FN) are patients predicted to not develop SIRS but who subsequently do develop SIRS. Among any set of patients for whom predictions are made, the accuracy statistic is the total number of correct predictions divided by the total number of predictions made. Thus, accuracy can be represented as (TP+TN)/(TP+FP+TN+FN). Accuracy, and the other statistics described and used here, are often represented as a percentage (by multiplying by 100 and adding the percentage symbol). Sensitivity is the fraction of patients who subsequently develop SIRS who are correctly predicted, and can be represented as TP/(TP+FN). Specificity is the fraction of patients who subsequently do not develop SIRS who are correctly predicted, and can be represented as TN/(TN+FP). Positive predictive value (PPV) is the fraction of positive predictions that are correct, and can be represented as TP/(TP+FP). Negative predictive value (NPV) is the fraction of negative predictions that are correct, and can be represented as TN/(TN+FN). Area under the curve (AUC) is the area under the receiver operating characteristic (ROC) curve, which is a plot of sensitivity, on the y-axis, against (1-specificity), on the x-axis, as the discrimination threshold is varied. It is a non-negative quantity whose maximum value is one. Different machine learning methods have their own mechanism of varying the discrimination threshold. In logistic regression that can be

achieved by changing the threshold probability between calling a prediction negative and positive (nominally 0.5), for example by progressively varying it from zero to one, which then maps out the ROC curve.

Together, this evidence shows that the features in **Table 4** have value in machine learning prediction of patients who will and who will not develop SIRS in the next 6-to-48 hours, and that other features in the dataset do not. That is, these features selected by the feature selection method described above, when applied to a machine learning algorithm, cause the machine learning algorithm to generate a good prediction model, the prediction model accepting patient-specific values for those selected features to predict likelihood of the respective specific patients developing SIRS.

Table 2. Results for four separate sets of calculations are presented. Each calculation used data from a different set of data from MIMIC II (collected 6, 12, 24, or 48 hours in advanced of the onset of SIRS for the positive patients). For each of the four sets of calculations, the results show that using only the data associated with the features in **Table 4** (all primary and secondary features associated with that time point), accurate predictions could be made regarding which patients would and which would not develop SIRS, as judged by statistical measures familiar to the machine learning community such as accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). In addition, the true positive rate (TP), true negative rate (TN), false positive rate (FP), and false negative rate (FN) are given. Parallel experiments using only data that were associated with features not primary or secondary for that time point ("remaining features") were unable to make accurate predictions regarding which patients would and which would not develop SIRS at the selected time This is indicated by an area under the curve of very close to 50%.

	Using only primary and secondary features at time point	**Using only remaining features (not primary or secondary) at time point**
6-hour dataset	Accuracy=82.01% Sensitivity=90.87% Specificity=54.80% PPV=86.07% NPV=66.14% TP=68.56% TN=13.45% FP=11.09% FN=6.88% AUC=72.84%	Specificity=0.30% AUC=50.03%
12-hour dataset	Accuracy=81.29% Sensitivity=87.09% Specificity=66.34% PPV=86.96% NPV=66.60%	Specificity=4.79% AUC=50.91%

	Using only primary and secondary features at time point	Using only remaining features (not primary or secondary) at time point
	TP=62.75% TN=18.53% FP=9.40% FN=9.29% AUC=76.71%	
24-hour dataset	Accuracy=82.02% Sensitivity=85.96% Specificity=73.81% PPV=87.26% NPV=71.57% TP=58.12% TN=23.90% FP=8.47% FN=9.49% AUC=79.88%	Specificity=0.0% AUC=50.0%
48-hour dataset	Accuracy=84.55% Sensitivity=84.73% Specificity=84.26% PPV=90.10% NPV=76.54% TP=53.25% TN=31.30% FP=5.84% FN=9.59% AUC=84.49%	Specificity=0.0% AUC=50.0%

An example of a poorly predictive model with area under the curve of 50% is shown in **Table 3** (48-hour data, remaining features only [not primary features for 48-hour data, not secondary features for 48-hour data, and not features removed in the Bhattacharyya procedure]). Most of the features have a coefficient value of zero, indicative of model that had difficulty learning from the training data. This indicates that the remaining features set, listed in the Table 3, was not sufficiently informative to predict SIRS occurrence.

Table 3. This is an example of a model that is poorly predictive of SIRS occurrence. The features are listed in the first column (except for the first row, which contains the model bias), and the coefficients w_j in the model are shown in the third column. The middle column contains a brief description of each feature.

Feature ID	Brief Feature Description	Coefficient Value
Bias	(b in model)	0.182399577
chart 2	ABI (L)	0

Feature ID	Brief Feature Description	Coefficient Value
chart 4	ABI Ankle BP R/L	0
chart 5	ABI Brachial BP R/L	0
chart 25	AV Interval	0
chart 26	AaDO2	0
chart 29	Access mmHg	0
chart 63	BIPAP - BPM	0
chart 65	BIPAP - Est. Vt	0
chart 79	Blood Flow ml/min	0
chart 92	CPP	0
chart 142	Current Goal	0
chart 146	Dialysate Flow ml/hr	0
chart 181	Epidural Total Dose	0
chart 186	FIO2 Alarm-Low	0
chart 192	Filter Pressure mmHg	0
chart 221	I:E Ratio	0
chart 226	ICP	0
chart 440	MDI #2 (Puff/Drug)	0
chart 441	MDI #3 (Puff/Drug)	0
chart 442	Manual BP	0
chart 449	Minute Volume (Set)	0
chart 472	O2AV	0
chart 473	O2AVI	0
chart 481	Orthostat HR sitting	0
chart 482	OrthostatBP standing	0
chart 483	OrthostatHR standing	0
chart 484	Orthostatic BP lying	0
chart 485	Orthostatic HR lying	0
chart 490	PAO2	0
chart 491	PAP Mean	0
chart 492	PAP S/D	0
chart 494	PCA Basal Rate	0
chart 496	PCA Dose	0
chart 498	PCA Lockout (Min)	0
chart 503	PCV Set Insp. Press	0
chart 512	PVR	0
chart 517	Pacer Rate	0
chart 595	RSBI (<200)	0
chart 601	RVSW	0
chart 602	RVSWI	0
chart 607	Rec.Breath Time(sec)	0
chart 624	Return Pressure mmHg	0
chart 626	SVR	0
chart 664	Swan SVO2	0
chart 670	TCPCV Insp. Pressure	0

Feature ID	Brief Feature Description	Coefficient Value
chart 671	TCPCV Insp. Time	0
chart 686	Total PEEP Level	0
chart 725	Vision - IPAP	0
chart 727	Vision FiO2	0
chart 773	Alk. Phosphate	0
chart 784	CPK	0
chart 792	Cyclosporin	0
chart 793	D-Dimer (0-500)	0
chart 809	Gentamycin/Random	0
chart 817	LDH	0
chart 826	Phenobarbital	0
chart 835	Sed Rate	0
chart 836	Serum Osmolality	0
chart 844	Thrombin (16-21)	0
chart 850	Triglyceride (0-200)	0
chart 851	Troponin	0
chart 856	Vancomycin/Trough	0
chart 1223	HIGH EXHALED MIN VOL	0
chart 1340	high minute volume	0
chart 1390	DO2	0
chart 1391	DO2I	0
chart 1397	RSBI (<100)	0
chart 1401	zzO2AV	0
chart 1402	zzO2AVI	0
chart 1411	Bladder Pressure	0
chart 1486	High Minute Volume	0
chart 1520	ACT	0
chart 1524	Cholesterol	0
chart 1526	D-Dimer	0
chart 1528	Fibrinogen	0
chart 1537	Thrombin	0
chart 1540	Triglyceride	0
chart 1546	high ve	0
chart 1565	High MV Limit	0
chart 1624	PreSep Catheter SVO2	0
chart 1671	act	0
chart 2139	EDVI	0
chart 5683	Hourly PFR	0
chart 5816	ICP Alarm (Lo/Hi)	0
chart 5818	PAP Alarm (Lo/Hi)	0
chart 6702	Arterial BP Mean #2	0
chart 6711	INV#5 Cap Change	0
chart 6712	INV#5 Tubing Change	0
lab 50001	AADO2	0

Feature ID	Brief Feature Description	Coefficient Value
lab 50013	O2	0
lab 50038	AMYLASE	0
lab 50042	CREAT	0
lab 50044	LD(LDH)	0
lab 50055	%phenyfr	0
lab 50056	ACETMNPHN	0
lab 50059	AFP	0
lab 50061	ALK PHOS	0
lab 50062	ALT(SGPT)	0
lab 50064	AMMONIA	0
lab 50071	ANTITPO	0
lab 50072	ASA	0
lab 50073	AST(SGOT)	0
lab 50075	C3	0
lab 50076	C4	0
lab 50077	CA125	0
lab 50078	CA27.29	0
lab 50082	CEA	0
lab 50086	CK(CPK)	0
lab 50087	CK-MB	0
lab 50089	CORTISOL	0
lab 50093	CYCLSPRN	0
lab 50094	DHEA-SO4	0
lab 50098	ESTRADL	0
lab 50099	ETHANOL	0
lab 50101	FERRITIN	0
lab 50102	FK506	0
lab 50106	FSH	0
lab 50107	GASTRIN	0
lab 50109	GGT	0
lab 50115	HAPTOGLOB	0
lab 50120	HCG	0
lab 50129	IgA	0
lab 50130	IgG	0
lab 50138	LIPASE	0
lab 50144	OSMOLAL	0
lab 50146	PHENOBARB	0
lab 50152	PROLACTIN	0
lab 50154	PTH	0
lab 50158	RHEU FACT	0
lab 50164	T4Index	0
lab 50165	TESTOSTER	0
lab 50167	THYROGLB	0
lab 50173	TRF	0

Feature ID	Brief Feature Description	Coefficient Value
lab 50179	VALPROATE	0
lab 50181	VIT B12	0
lab 50190	calTIBC	0
lab 50195	proBNP	0
lab 50196	rapamycin	0
lab 50202	LD(LDH)	0
lab 50204	PROTEIN	0
lab 50208	GLUCOSE	0
lab 50212	AMYLASE	0
lab 50216	CREAT	0
lab 50217	GLUCOSE	0
lab 50218	LD(LDH)	0
lab 50225	POTASSIUM	0
lab 50226	SODIUM	0
lab 50232	UREA N	0
lab 50235	AMYLASE	0
lab 50237	CHOLEST	0
lab 50239	CREAT	0
lab 50240	GLUCOSE	0
lab 50241	LD(LDH)	0
lab 50247	TRIGLYCER	0
lab 50250	OSMOLAL	0
lab 50251	POTASSIUM	0
lab 50252	SODIUM	0
lab 50253	24Ca++	0
lab 50254	24Creat	0
lab 50255	24Prot	0
lab 50258	<CREAT-U>	0
lab 50259	<VOL-U>	0
lab 50260	AMY/CREAT	0
lab 50261	AMYLASE	0
lab 50263	CHLORIDE	0
lab 50265	CREAT CLR	0
lab 50266	GLUCOSE	0
lab 50273	PHOSPHATE	0
lab 50276	PROT/CREA	0
lab 50277	SODIUM	0
lab 50278	TOT PROT	0
lab 50279	TOTAL CO2	0
lab 50284	URIC ACID	0
lab 50285	VOLUME	0
lab 50287	alb/CREA	0
lab 50288	albumin	0
lab 50302	HCT	0

Feature ID	Brief Feature Description	Coefficient Value
lab 50304	MACROPHAG	0
lab 50313	RBC	0
lab 50314	WBC	0
lab 50317	ABS CD3	0
lab 50318	ABS CD4	0
lab 50319	ABS CD8	0
lab 50320	ABS LYMPH	0
lab 50322	ACA IgG	0
lab 50323	ACA IgM	0
lab 50330	AT III	0
lab 50335	BLASTS	0
lab 50356	CD4	0
lab 50357	CD4/CD8	0
lab 50367	CD8	0
lab 50374	EOS CT	0
lab 50378	FIBRINOGE	0
lab 50382	GRAN CT	0
lab 50385	HEPARIN	0
lab 50390	HGB F	0
lab 50395	HYPERSEG	0
lab 50404	LAP	0
lab 50427	PLASMA	0
lab 50428	PLT COUNT	0
lab 50434	PROMYELO	0
lab 50436	PROT C FN	0
lab 50437	PROT S AG	0
lab 50438	PROT S FN	0
lab 50441	QUAN G6PD	0
lab 50451	SED RATE	0
lab 50460	THROMBN	0
lab 50461	V	0
lab 50463	VIII	0
lab 50465	VWF AG	0
lab 50466	VWF CO	0
lab 50469	X	0
lab 50473	YOUNG	0
lab 50510	BANDS	0
lab 50511	BASOS	0
lab 50513	EOS	0
lab 50526	RBC	0
lab 50530	BANDS	0
lab 50537	LYMPHS	0
lab 50541	MONOS	0
lab 50545	POLYS	0

Feature ID	Brief Feature Description	Coefficient Value
lab 50546	RBC	0
lab 50548	WBC	0
lab 50549	ATYPS	0
lab 50550	BANDS	0
lab 50551	BASOS	0
lab 50560	CD19	0
lab 50565	CD3	0
lab 50567	CD34	0
lab 50579	EOS	0
lab 50587	LYMPHS	0
lab 50588	MACROPHAG	0
lab 50589	MESOTHELI	0
lab 50598	RBC	0
lab 50599	WBC	0
lab 50600	ATYPS	0
lab 50603	EOS	0
lab 50604	HCT	0
lab 50609	MONOS	0
lab 50614	POLYS	0
lab 50616	RBC	0
lab 50617	WBC	0
lab 50632	CELL	0
lab 50641	GLUCOSE	0
lab 50647	KETONE	0
lab 50652	NSQ EPI	0
lab 50655	PROTEIN	0
lab 50659	RENAL EPI	0
lab 50664	TRANS EPI	0
lab 50675	WBCCAST	0
lab 50687	MS-AFP	0
lab 50689	MS-HCG	0
lab 50690	MS-UE3	0
lab 50699	tacroFK	0
io 48	Chest Tubes Left Pleural 1	0
io 49	Chest Tubes Right Pleural 1	0
io 51	Gastric Gastric Tube	0
io 52	Gastric Nasogastric	0
io 53	Stool Out Fecal Bag	0
io 58	Cerebral Drain R Ventricular Drain	0
io 59	Gastric Oral Gastric	0
io 60	Pre-Admission Output Pre-Admission Output	0
io 61	OR Out OR Urine	0
io 63	Stool Out Ileostomy	0
io 64	OR Out EBL	0

Feature ID	Brief Feature Description	Coefficient Value
io 65	OR Out PACU Urine	0
io 66	Drain Out #1 Tap	0
io 68	Stool Out Other	0
io 70	Drain Out #1 Hemovac	0
io 71	Drain Out #1 Jackson Pratt	0
io 72	Drain Out #2 Jackson Pratt	0
io 73	PACU Out PACU Drains	0
io 74	PACU Out PACU NG	0
io 76	Chest Tubes CTICU CT 1	0
io 77	Drain Out #1 Pericardial	0
io 80	Drain Out #2 Other	0
io 84	Chest Tubes Other	0
io 85	Urine Out Incontinent	0
io 87	Stool Out Colostomy	0
io 88	Drain Out #3 Jackson Pratt	0
io 91	Chest Tubes Mediastinal	0
io 92	Drain Out #4 Jackson Pratt	0
io 93	Drain Out #1 T Tube	0
io 94	Urine Out Condom Cath	0
io 104	D5W 100.0ml	-0.029107698
io 106	Lactated Ringers	0
io 107	0.9% Normal Saline	0
io 123	OR Colloid	0
io 124	OR Crystalloid	0
io 125	PACU Crystalloids	0
io 128	TF Residual	0
io 130	D5/.45NS	0
io 131	D5/.45NS 10000.0ml	0
io 132	D5W 50.0ml	0
io 137	D5W 250.0ml + 25000Uhr Heparin	0
io 138	D5W 125.0ml + 125mghr Diltiazem	0
io 139	Sterile Water 100.0ml	0
io 140	D5W 250.0ml + 400mcgkgmin Dopamine	0
io 141	N/A 50.0vl + 500mcgkgmin Propofol	0
io 142	Lactated Ringers 1000.0ml	0
io 143	Dextrose 10%	0
io 144	Packed RBC's	0
io 147	D5W 250.0ml + 100mcgmin Nitroglycerine	0
io 149	N/A 100.0vl + 1000mcgkgmin Propofol	0
io 151	.45% Normal Saline 1000.0ml	0
io 152	D5/.45NS 1000.0ml	0
io 154	D5NS	0
io 155	Gastric Meds	0
io 158	OR FFP	0

Feature ID	Brief Feature Description	Coefficient Value
io 159	PACU Colloids	0
io 161	D5W 250.0ml + 60mcgmin Neosynephrine	0
io 162	D5W 200.0ml + 20mghr Ativan	0
io 163	Fresh Frozen Plasma	0
io 165	D5W 1000.0ml	0
io 168	D5W	0
io 172	OR Packed RBC's	0
io 173	D5W 100.0ml + 100mghr Morphine Sulfate	0
io 174	D5W 250.0ml + 600mgmin Amiodarone	0
io 178	D5W 250.0ml + 50mcgkgmin Nitroprusside	0
io 179	Platelets	0
io 180	0.45% Normal Saline	0
io 182	Nepro	0
io 183	PPN	0
io 186	TPN 1000.0ml	0
io 187	0.9% Normal Saline 500.0ml	0
io 191	Replete w/fiber	0
io 192	Carrier 1000.0ml	0
io 202	D5W 250.0ml + 2mcgkgmin Epinephrine-k	0
io 211	0.9% Normal Saline 100.0ml + 100Uhr Insulin	0
io 212	D5W 250.0ml + 12.5mcgkgmin Aggrastat	0
io 213	D5W 250.0ml + 4mcgkgmin Levophed-k	0
io 214	D5 Normal Saline	0
io 215	D5W 250.0ml + 100mcgkgmin Nitroprusside	0
io 218	D5W 250.0ml + 60mcgkgmin Neosynephrine-k	0
io 219	D5RL 1000.0ml	0
io 222	Impact w/fiber	0
io 224	OR Platelets	0
io 225	0.9% Normal Saline 100.0ml + 100mgmin Labetolol	0
io 232	Albumin 5%	0
io 241	D5W 250.0ml + 100mcgkgmin Cisatracurium + 100 mg kg hr Cisatracurium	0
io 246	Hespan	0
io 249	0.9% Normal Saline 250.0ml	0
io 250	D5W 250.0ml + 20mcgkgmin Neosynephrine-k	0
io 256	D5W 250.0ml + 250mcgkgmin Dobutamine	0
io 258	Albumin 25%	0
io 264	D5W 100.0ml + 20mcgkgmin Milrinone	0
io 272	TPN w/Lipids	0
io 274	Free Water Bolus	0
io 276	D5W 200.0ml	0
io 286	Ultrafiltrate Ultrafiltrate	0
io 294	Drain Out #1 Other	0
io 297	D5NS 1000.0ml	0

Feature ID	Brief Feature Description	Coefficient Value
io 299	D5 Normal Saline 1000.0ml	0
io 309	0.9% Normal Saline 100.0ml	0
io 319	Cryoprecipitate	0
io 331	Gastric Jejunostomy Tube	0
io 336	Cell Saver	0
io 346	Dextrose 10% 1000.0ml	0
io 353	D5W 100.0ml + 100mghr Lasix	0
io 362	D5W 500.0ml	0
io 367	Stool Out Rectal Tube	0
io 370	Tube Feeding	0
io 372	D5W 250.0ml + 16mcgkgmin Levophed-k	0
io 375	D5W 250.0ml + 8mcgkgmin Levophed-k	0
io 388	Stool Out (non-specific)	0
io 393	D5W 500.0ml + 2mgmin Lidocaine	0
io 397	Washed PRBC's	0
io 398	Packed RBC's 375.0ml	0
io 406	Gastric Other	0
io 411	D5W 50.0ml + 100mghr Lasix	0
io 414	0.9% Normal Saline 200.0ml + 200mgmin Labetolol	0
io 415	Carrier 250.0ml	0
io 436	D5W 300.0ml + 1200mgmin Labetolol	0
io 454	D5W 250.0ml + 9mcgkgmin Reopro + 9mcgmin Reopro	0
io 473	Urine Out IleoConduit	0
io 474	0.9% Normal Saline 100.0ml + 200mgmin Labetolol	0
io 477	Sterile Water 100.0ml + 100mgmin TPA	0
io 481	Promote w/fiber	0
io 491	PACU Out EBL	0
io 496	D5W 250.0ml + 120mcgkgmin Neosynephrine-k	0
io 518	D5 Ringers Lact. 1000.0ml	0
io 537	Cerebral Drain Subdural	0
io 541	D5W 500.0ml + 2mcgkgmin Narcan	0
io 555	Promote	0
io 563	0.9% Normal Saline 300.0ml + 1200mgmin Labetolol	0
io 580	Cath Lab Output	0
io 591	Normal Saline_GU	0
io 615	D5/.45NS 2000.0ml	0
io 648	Drain Out #3 Other	0
io 659	Other Blood Products	0
io 703	Drain Out #1 JP Lateral	0
io 715	Urine Out Suprapubic	0
io 761	D5W 250.0ml + 1.5mcgkgmin Natrecor	0
io 781	0.45% Normal Saline 2000.0ml	0
io 898	D5/.45NS 999.0ml	0
io 900	0.9% Normal Saline 200.0ml + 600mgmin Labetolol	0

Feature ID	Brief Feature Description	Coefficient Value
io 926	Drain Out #1 JP Medial	0
io 1101	Protonix	0
io 1683	Drain Out #2 JP Lateral	0
io 1698	Drain Out #2 Hemovac	0
io 1707	Chest Tubes CTICU CT 2	0
io 1867	Drain Out #1 Lumbar	0
io 1883	0.9% Normal Saline 250.0ml + 25mcgkgmin Nicardipine	0
io 1898	Drain Out #3 T Tube	0
io 3680	ProBalance	0
io 3692	0.9% Normal Saline 250.0ml + 125mcgkgmin Nicardipine	0
io 4691	D5W 250.0ml + 100Uhr Vasopressin + 100Umin Vasopressin	0
io 4692	D5W 250.0ml + 200Uhr Vasopressin + 200Umin Vasopressin	0
med 25	Heparin	0
med 47	Levophed	0
med 49	Nitroglycerine	0
med 115	Diltiazem	0
med 118	Fentanyl	0
med 120	Levophed-k	0
med 123	Lasix	0
med 126	Morphine Sulfate	0
med 127	Neosynephrine	0
med 133	Sandostatin	0
med 134	Reopro	0
med 163	Dilaudid	0
totalbal 3	Blood Products Total	0
totalbal 4	Cerebral Drain Total	0
totalbal 5	Chest Tube Out Total	0
totalbal 6	Colloids Total	0
totalbal 7	Drain #1 Total Out	0
totalbal 8	Drain #2 Total Out	0
totalbal 9	Drain #3 Total Out	0
totalbal 10	Drain #4 Total Out	0
totalbal 24	Tube Feeds In Total	0
totalbal 25	UltrafiltrateTotal	0
totalbal 27	24h Net Body Balance	0
totalbal 28	LOS Net Body Balance	-0.010032666

From the 48-hour dataset, 32 features in total were selected (20 primaries and 12 secondaries; some of the primary features had no associated secondary features). Each primary feature and its associated secondary features (if any) made up a "feature group," giving 20 initial feature groups. An additional 16 features total were added to this feature set to optimize

performance on the 6-, 12-, and 24-hour datasets. For example, feature groups that were selected for a different onset period can be selected. These additional features made up a 21st feature group, called "additional" features. For example, in an example embodiment, the system applies the feature selection method described above based on data associated with positives and negatives of developing a disease within each of a plurality of time frames, to identify respective relevant subsets of features for predicting onset of the disease in the respective time frame. This may result in identification of a feature subset as relevant for predicting onset within a first of the time frames, which feature subset had not been identified as relevant for predicting onset within one or more others of the time frames. Nevertheless, in an example embodiment, even if a feature subset had not been selected for prediction of onset within a particular time frame, if the feature subset had been selected for a different time frame, it is used for training a prediction model even for the time frame for which it had not been selected. (If it is subsequently determined that the generated model does not yield satisfactory prediction results for the time frame, then it is discarded as it relates to that time frame.)

Table 4 shows the selected features organized by feature group, including their identifier in the MIMIC II database, the role they play (as primary, secondary, or additional features), and a brief description. Using a separate database, the same procedure as detailed above could be used to identify and select primary and secondary features and additional features from that separate database, using the above methods of the invention, which is within the scope of the invention. Likewise, such separate measurements are within the meaning of the term "feature" as used in this application. Further, as explained above, if a given hospital measures a feature in different units or uses a different type of measurement for the same feature as compared to the MIMIC II database, those data are also "features" as defined herein and can be used in the above selection and prediction methods of the invention, which is within the scope of the invention. As used herein, a "MIMIC II feature" is a feature (whether primary, secondary, additional or remaining) from the MIMIC II database, while a "feature" includes such MIMIC II features and other features that may be identified and/or selected from other hospital databases, in accordance with the invention and as described herein. Such features from other databases are also termed primary, secondary, additional and remaining in accordance with the methods of the invention.

Table 4. Feature groups selected in this work. Each row of the table indicates a different feature. The first column lists the feature group by number to which the feature is associated. The second column lists the feature by it identifier in the MIMIC II database and how it was selected (as a 48-hour primary or secondary feature, or as an additional feature). The third column gives a brief description of what the feature measures, which has a well-known meaning to a person of ordinary skill in the art.

Feature Group	**Feature Identifier (role)**	**Brief Feature Description**
1	chart 818 (1st primary)	Lactic Acid (0.5-2.0)
1	chart 1531 (secondary to 1st primary)	Lactic Acid
2	chart 781 (2nd primary)	BUN (6-20)
2	chart 1162 (secondary to 2nd primary)	BUN; Blood Urea Nitrogen
3	chart 828 (3rd primary)	Platelets
3	chart 811(secondary to 3rd primary)	Glucose (70-105)
3	chart 1529 (secondary to 3rd primary)	Glucose
4	totalbal 20 (4th primary)	PO/Gastric In Total
4	io 102 (secondary to 4th primary)	Po Intake
5	lab 50019 (5th primary)	PO2
5	chart 779 (secondary to 5th primary)	Arterial PaO2
6	totalbal 26 (6th primary)	Urine Out Total
6	totalbal 2 (secondary to 6th primary)	24-hr Total Out
6	totalbal 18 (secondary to 6th primary)	IV Infusion In Total
6	io 55 (secondary to 6th primary)	Urine Out Foley
7	totalbal 19 (7th primary)	IV Nutrition Total
8	chart 682 (8th primary)	Tidal Volume (Observ.) Lung Vol. Displac.
9	chart 785 (9th primary)	CPK/MB Blood Test
10	io 97 (10th primary)	Cerebral Drain L Ventricular Drain
11	lab 50017 (11th primary)	PEEP; positive end respiratory pressure
12	totalbal 1 (12th primary)	24-hr Total In
13	totalbal 16 (13th primary)	Gastric Out Total
14	io 133 (14th primary)	D5W 250.0 ml + 100 mcg/kg/min Nitroglycerine-k
15	chart 683 (15th primary)	Tidal Volume (Set)
16	chart 789 (16th primary)	Cholesterol (< 200)
17	chart 807 (17th primary)	Fingerstick Glucose
18	chart 815 (18th primary)	INR (2–4 ref. range)
18	chart 821 (secondary to 18th primary)	Magnesium (1.6–2.6)

Feature Group	Feature Identifier (role)	Brief Feature Description
18	chart 1532 (secondary to 18th primary)	Magnesium
18	lab 50030 (secondary to 18th primary)	free Ca
19	io 134 (19th primary)	0.9% Normal Saline 1000 ml
20	totalbal 23 (20th primary)	Total Hourly Output
21	chart 1528 (additional)	Fibrinogen
21	chart 198 (additional)	GCS Total Glasgow Coma Scale
21	chart 20001 (additional)	SAPS-I Simplified Acute Physiology Score
21	chart 20009 (additional)	Overall SOFA (Sequen. Organ Failure) Score
21	chart 211 (additional)	Heart Rate
21	chart 671 (additional)	TCPCV Insp. Time Ventilation
21	chart 773 (additional)	Alk. Phosphate
21	chart 793 (additional)	D-Dimer (0-500)
21	chart 809 (additional)	Gentamycin/Random
21	chart 826 (additional)	Phenobarbital
21	chart 856 (additional)	Vancomycin/Trough
21	chart 87 (additional)	Braden Score
21	io 53 (additional)	Stool Out Fecal Bag
21	io 69 (additional)	Urine Out Void
21	med 163 (additional)	Dilaudid
21	totalbal 25 (additional)	UltrafiltrateTotal

Example 2: Different Combinations of Patients Produce Models with Similarly High Predictive Accuracy.

Because the features within the first 20 feature groups are correlated with each other (especially within feature groups with more than one feature), the inventors carried out a further set of experiments in which we chose two features from each of the first 14 feature sets (but only one feature from feature sets that had only one feature) and two features from the additional set, and tested their predictive ability. Ten independent experiments of this type were carried out using the same features used in the model, but different random divisions of the data into training and testing data. Machine learning as above on the training sets was used to create a model that was then tested on the testing set (containing the patients the model had not seen). The scores on each of ten the testing set are reported in **Table 5** for each of the four time points, together with the features in that dataset and the predictive model resulting from the training that produced these results. The results show all of the models have very good

predictive capabilities, even though each of the respective models may differ from one another. This is consistent with the features being powerfully useful for accurate prediction.

Table 5. The parameters for forty different predictive models are given (ten different sets of parameters each used for the four different time points) together with the performance of those models. Each of the ten parameter sets appears in its own section of the table, followed by the predictive performance of those model parameters. In each set of parameters, the first parameter given is the bias, followed by the coefficient for each of the features from MIMIC II, for the four different models at four different time points in advance of the onset of SIRS in the positive set. Positive coefficients indicate a tendency of the respective parameter predicting being tested positive for SIRS and negative coefficients indicate a tendency of the respective parameter predicting being tested negative for SIRS.

	48-hour model	**24-hour model**	**12-hour model**	**6-hour model**
Set 1 Parameters				
bias	0.615920	0.913224	1.045310	1.196787
chart 1162	-0.079121	-0.057250	0.000000	0.000000
chart 1528	0.014627	-0.011422	-0.010567	0.028798
chart 1531	-0.079470	-0.117308	-0.119365	-0.081314
chart 198	0.000000	-0.623604	-0.602151	-0.434176
chart 682	0.129793	0.172320	0.145261	0.000000
chart 779	0.059285	0.000000	0.149554	0.276046
chart 781	0.083009	0.110677	0.035790	0.000000
chart 785	-0.051666	0.043012	0.000000	0.000000
chart 811	-0.583528	-0.265289	-0.314617	-0.173928
chart 818	-0.048873	0.000000	0.000000	0.000000
chart 828	-0.633149	-0.374788	0.000000	-0.228734
io 102	0.115260	0.108089	0.066090	0.061826
io 133	0.078115	0.073909	0.093805	0.000000
io 97	0.013388	-0.002194	0.011098	0.063874
lab 50017	0.061014	0.000000	0.000000	0.000000
lab 50019	-0.159398	-0.073326	-0.024099	0.121263
totalbal 1	-0.119435	0.015848	0.055107	0.079042
totalbal 16	0.014986	-0.020905	-0.044861	-0.046192
totalbal 19	0.019590	0.033700	0.013719	0.008559
totalbal 2	-0.116085	0.000000	-0.058382	-0.036658
totalbal 20	-0.340788	-0.307695	-0.382889	-0.424959
totalbal 26	-0.405579	-0.358916	-0.317020	-0.327842
Set 1 Predictive Results				
Accuracy	83.95%	81.47%	81.03%	81.15%
PPV	87.71%	86.66%	84.71%	84.16%
Sensitivity	86.65%	86.10%	89.75%	92.34%
Specificity	79.35%	71.54%	58.93%	47.01%
NPV	77.76%	70.56%	69.40%	66.82%
AUC	83.00%	78.82%	74.34%	69.68%

	48-hour model	24-hour model	12-hour model	6-hour model
Set 2 Parameters				
bias	0.59695573	0.909521	1.057665	1.229083
chart 1162	0.082354	0.034969	0.000000	0.000000
chart 1529	-0.384999	-0.174643	-0.171213	-0.074010
chart 1531	-0.031844	-0.103458	-0.090403	-0.040508
chart 198	0.000000	-0.605356	-0.586906	-0.396961
chart 20001	0.000000	-0.288058	-0.473570	-0.439801
chart 682	0.115831	0.216234	0.227728	0.000000
chart 779	0.029516	0.000000	0.138712	0.312833
chart 781	-0.087739	0.051992	0.071431	0.000000
chart 785	-0.066235	0.025113	0.000000	0.000000
chart 818	-0.084714	0.000000	0.000000	0.000000
chart 828	-0.725970	-0.381094	0.000000	-0.220024
io 102	0.104973	0.112235	0.076689	0.071534
io 133	0.074103	0.086076	0.112418	0.000000
io 97	0.019507	-0.003578	0.010001	0.058538
lab 50017	0.064066	0.000000	0.000000	0.000000
lab 50019	-0.178200	-0.080493	-0.034266	0.133420
totalbal 1	-0.096806	0.066154	0.110757	0.171955
totalbal 16	0.029085	-0.001094	-0.010024	-0.001588
totalbal 18	-0.171826	-0.054175	-0.047516	-0.048636
totalbal 19	0.018322	0.039806	0.023564	0.016940
totalbal 20	-0.354524	-0.278917	-0.325748	-0.364174
totalbal 26	-0.480544	-0.285616	-0.254159	-0.245701
Set 2 Predictive Results				
Accuracy	83.61%	82.11%	81.86%	82.09%
PPV	87.10%	86.94%	86.17%	86.25%
Sensitivity	86.83%	86.82%	88.99%	90.67%
Specificity	78.14%	72.00%	63.81%	55.94%
NPV	77.73%	71.78%	69.56%	66.29%
AUC	82.49%	79.41%	76.40%	73.30%
Set 3 Parameters				
bias	0.61676526	0.869603	1.016045	1.201040
chart 1162	-0.074871	-0.041301	0.000000	0.000000
chart 1531	-0.079106	-0.040634	-0.043314	-0.017709
chart 20001	0.000000	-0.228548	-0.418474	-0.399840
chart 20009	0.000000	-0.296936	-0.272117	-0.158803
chart 682	0.105667	0.299904	0.319713	0.000000
chart 779	0.047056	0.000000	0.186297	0.359814
chart 781	0.068296	0.138811	0.098510	0.000000
chart 785	-0.046401	0.018356	0.000000	0.000000

	48-hour model	24-hour model	12-hour model	6-hour model
chart 811	-0.573524	-0.354420	-0.467158	-0.217760
chart 818	-0.052816	0.000000	0.000000	0.000000
chart 828	-0.630249	-0.520801	0.000000	-0.305409
io 102	0.042085	0.021683	-0.028267	-0.023195
io 133	0.065330	0.071635	0.111925	0.000000
io 55	0.258612	0.279953	0.234635	0.248006
io 97	0.013375	-0.002941	0.016216	0.049905
lab 50017	0.050744	0.000000	0.000000	0.000000
lab 50019	-0.158154	-0.037681	-0.001000	0.169138
totalbal 1	-0.163007	0.033040	0.084071	0.149264
totalbal 16	-0.000048	0.012147	-0.010687	-0.002006
totalbal 19	0.009974	0.041029	0.025875	0.009955
totalbal 20	-0.306671	-0.325202	-0.361284	-0.372054
totalbal 26	-0.595502	-0.578033	-0.511842	-0.455543
Set 3 Predictive Results				
Accuracy	83.87%	82.50%	79.98%	80.83%
PPV	87.76%	86.75%	84.20%	84.92%
Sensitivity	86.43%	87.75%	88.74%	90.64%
Specificity	79.50%	71.23%	57.77%	50.92%
NPV	77.51%	73.04%	66.94%	64.09%
AUC	82.97%	79.49%	73.26%	70.78%
Set 4 Parameters				
bias	0.59725842	0.857635	1.027098	1.188486
chart 1162	0.088805	0.077187	0.000000	0.000000
chart 1529	-0.388303	-0.253960	-0.242489	-0.122255
chart 1531	-0.031446	-0.011477	-0.016946	-0.006168
chart 20009	0.000000	-0.406286	-0.454881	-0.366385
chart 211	0.000000	0.000000	-0.477251	-0.113969
chart 682	0.116333	0.308925	0.390253	0.000000
chart 779	0.032301	0.000000	0.134304	0.353429
chart 781	-0.093651	0.026673	0.087839	0.000000
chart 785	-0.065092	-0.002758	0.000000	0.000000
chart 818	-0.090451	0.000000	0.000000	0.000000
chart 828	-0.739739	-0.617315	0.000000	-0.362596
io 102	0.119758	0.082825	0.038018	0.040678
io 133	0.075430	0.075379	0.092312	0.000000
io 97	0.017009	0.012403	0.023001	0.065841
lab 50017	0.061409	0.000000	0.000000	0.000000
lab 50019	-0.179407	-0.064676	-0.024317	0.154678
totalbal 1	-0.150346	0.001785	0.122049	0.148969
totalbal 16	0.021809	0.022513	-0.006013	0.006992
totalbal 19	0.020089	0.052639	0.029443	0.023396
totalbal 2	-0.135348	0.000000	-0.074924	-0.033416

	48-hour model	24-hour model	12-hour model	6-hour model
totalbal 20	-0.354069	-0.393439	-0.407032	-0.457152
totalbal 26	-0.438391	-0.510071	-0.373762	-0.377456
Set 4 Predictive Results				
Accuracy	83.47%	81.84%	80.00%	80.18%
PPV	86.94%	85.65%	83.87%	83.97%
Sensitivity	86.79%	88.15%	89.29%	91.06%
Specificity	77.84%	68.29%	56.46%	47.01%
NPV	77.60%	72.85%	67.53%	63.30%
AUC	82.31%	78.22%	72.88%	69.04%
Set 5 Parameters				
bias	0.61450305	0.859746	1.014454	1.162259
chart 1162	-0.074703	-0.058870	0.000000	0.000000
chart 1531	-0.076971	-0.053235	-0.087837	-0.038245
chart 211	0.000000	0.000000	-0.410562	-0.107260
chart 671	0.102520	0.082216	0.074346	0.090695
chart 682	0.122927	0.208807	0.249759	0.000000
chart 779	0.062050	0.000000	0.170336	0.326798
chart 781	0.076803	0.042078	0.005781	0.000000
chart 785	-0.050517	0.024896	0.000000	0.000000
chart 811	-0.573466	-0.389515	-0.369917	-0.252222
chart 818	-0.046721	0.000000	0.000000	0.000000
chart 828	-0.626180	-0.507826	0.000000	-0.302875
io 102	0.102338	0.074418	0.027698	0.026270
io 133	0.077823	0.071404	0.084093	0.000000
io 97	0.014070	0.013240	0.022705	0.071831
lab 50017	0.048191	0.000000	0.000000	0.000000
lab 50019	-0.154367	-0.048937	-0.008529	0.153081
totalbal 1	-0.071973	0.035419	0.109590	0.149382
totalbal 16	0.024412	-0.001314	-0.039416	-0.030252
totalbal 18	-0.144695	-0.161657	-0.157742	-0.174891
totalbal 19	0.018760	0.035403	0.013320	0.009398
totalbal 20	-0.341943	-0.414468	-0.444812	-0.488835
totalbal 26	-0.450586	-0.493292	-0.391937	-0.382170
Set 5 Predictive Results				
Accuracy	84.09%	80.81%	79.74%	80.36%
PPV	87.91%	84.65%	83.05%	83.35%
Sensitivity	86.65%	87.79%	90.15%	92.37%
Specificity	79.73%	65.82%	53.36%	43.75%
NPV	77.84%	71.51%	68.11%	65.28%
AUC	83.19%	76.80%	71.76%	68.06%

	48-hour model	24-hour model	12-hour model	6-hour model
Set 6 Parameters				
bias	0.593348	0.844009	0.958029	1.141223
chart 1162	0.085433	0.066645	0.000000	0.000000
chart 1529	-0.383465	-0.256067	-0.316012	-0.165695
chart 1531	-0.032675	-0.053443	-0.024053	-0.029464
chart 671	0.101643	0.071712	0.067672	0.082138
chart 682	0.082330	0.156451	0.156465	0.000000
chart 773	0.039828	0.000000	0.000000	0.000000
chart 779	0.023593	0.000000	0.116854	0.262436
chart 781	-0.108960	-0.093785	-0.136490	0.000000
chart 785	-0.061386	0.013126	0.000000	0.000000
chart 818	-0.098447	0.000000	0.000000	0.000000
chart 828	-0.740965	-0.592884	0.000000	-0.392499
io 102	0.041260	0.025058	-0.009344	-0.016451
io 133	0.063383	0.059303	0.076644	0.000000
io 55	0.266610	0.236793	0.166960	0.162403
io 97	0.011900	0.004938	0.031009	0.061142
lab 50017	0.039830	0.000000	0.000000	0.000000
lab 50019	-0.172980	-0.079832	-0.030026	0.141330
totalbal 1	-0.196710	-0.073132	-0.042887	0.021993
totalbal 16	0.005866	-0.024535	-0.051521	-0.055779
totalbal 19	0.007636	0.024136	0.007213	-0.005093
totalbal 20	-0.323203	-0.398548	-0.489053	-0.477262
totalbal 26	-0.650986	-0.662500	-0.659062	-0.555817
Set 6 Predictive Results				
Accuracy	83.67%	80.71%	79.06%	80.30%
PPV	87.25%	84.24%	81.15%	83.06%
Sensitivity	86.74%	88.22%	92.22%	92.76%
Specificity	78.44%	64.58%	45.71%	42.31%
NPV	77.68%	71.86%	69.86%	65.72%
AUC	82.59%	76.40%	68.96%	67.54%
Set 7 Parameters				
bias	0.613974	0.858309	0.974021	1.150347
chart 1162	-0.077308	-0.060797	0.000000	0.000000
chart 1531	-0.080661	-0.054176	-0.057023	-0.038605
chart 682	0.131826	0.206607	0.185004	0.000000
chart 773	0.048919	0.000000	0.000000	0.000000
chart 779	0.062932	0.000000	0.182390	0.320940
chart 781	0.073781	0.044840	-0.046120	0.000000
chart 785	-0.051381	0.027303	0.000000	0.000000
chart 793	-0.009142	0.004290	-0.020299	-0.003593
chart 811	-0.588521	-0.395632	-0.506384	-0.285913
chart 818	-0.052222	0.000000	0.000000	0.000000

	48-hour model	24-hour model	12-hour model	6-hour model
chart 828	-0.639125	-0.517775	0.000000	-0.332109
io 102	0.113349	0.082236	0.039937	0.039174
io 133	0.078293	0.072124	0.086527	0.000000
io 97	0.013171	0.012923	0.027322	0.070743
lab 50017	0.060678	0.000000	0.000000	0.000000
lab 50019	-0.157873	-0.051702	-0.005444	0.154763
totalbal 1	-0.118569	-0.047450	0.008415	0.051431
totalbal 16	0.012901	-0.016717	-0.043213	-0.043930
totalbal 19	0.017418	0.034014	0.015434	0.009239
totalbal 2	-0.113743	0.000000	-0.105284	-0.054249
totalbal 20	-0.339247	-0.412832	-0.498335	-0.503869
totalbal 26	-0.403838	-0.536333	-0.453441	-0.408015
Set 7 Predictive Results				
Accuracy	83.98%	81.20%	79.09%	80.14%
PPV	87.78%	84.80%	81.70%	83.01%
Sensitivity	86.61%	88.26%	91.28%	92.58%
Specificity	79.50%	66.05%	48.18%	42.23%
NPV	77.74%	72.37%	68.54%	65.11%
AUC	83.06%	77.15%	69.73%	67.40%
Set 8 Parameters				
bias	0.596690	0.845004	0.962103	1.147989
chart 1162	0.081725	0.061713	0.000000	0.000000
chart 1529	-0.385030	-0.256333	-0.312654	-0.165197
chart 1531	-0.031393	-0.036796	-0.019196	-0.019240
chart 682	0.115715	0.197238	0.187996	0.000000
chart 779	0.029759	0.000000	0.126490	0.284521
chart 781	-0.086768	-0.085388	-0.123277	0.000000
chart 785	-0.065524	0.009114	0.000000	0.000000
chart 793	-0.006505	0.000326	-0.014960	-0.003230
chart 809	-0.030555	0.000000	0.000000	0.000000
chart 818	-0.084226	0.000000	0.000000	0.000000
chart 828	-0.725962	-0.578702	0.000000	-0.384182
io 102	0.105130	0.073824	0.031866	0.026925
io 133	0.074125	0.068055	0.077929	0.000000
io 97	0.020052	0.014244	0.031479	0.073195
lab 50017	0.064934	0.000000	0.000000	0.000000
lab 50019	-0.178624	-0.080260	-0.033336	0.142417
totalbal 1	-0.096818	0.018763	0.064525	0.128774
totalbal 16	0.029274	0.002096	-0.021955	-0.027764
totalbal 18	-0.171310	-0.173592	-0.209381	-0.187955
totalbal 19	0.018210	0.034869	0.014609	0.007114
totalbal 20	-0.354150	-0.419509	-0.518971	-0.508489
totalbal 26	-0.480792	-0.506810	-0.514822	-0.411002

	48-hour model	24-hour model	12-hour model	6-hour model
Set 8 Predictive Results				
Accuracy	83.59%	80.54%	78.69%	80.28%
PPV	87.07%	84.33%	81.27%	83.11%
Sensitivity	86.83%	87.79%	91.34%	92.63%
Specificity	78.06%	64.97%	46.64%	42.63%
NPV	77.71%	71.25%	67.98%	65.48%
AUC	82.45%	76.38%	68.99%	67.63%
Set 9 Parameters				
bias	0.616284	0.856007	0.973617	1.146810
chart 1162	-0.075573	-0.052118	0.000000	0.000000
chart 1531	-0.078892	-0.061977	-0.064236	-0.046893
chart 682	0.105076	0.175308	0.162112	0.000000
chart 779	0.047354	0.000000	0.172271	0.302153
chart 781	0.069215	0.037245	-0.050473	0.000000
chart 785	-0.045371	0.032464	0.000000	0.000000
chart 809	-0.021142	0.000000	0.000000	0.000000
chart 811	-0.572875	-0.394216	-0.505004	-0.283510
chart 818	-0.052810	0.000000	0.000000	0.000000
chart 826	0.025027	0.030628	0.023386	0.010586
chart 828	-0.630778	-0.520479	0.000000	-0.330871
io 102	0.042961	0.022472	-0.017407	-0.017328
io 133	0.065725	0.061135	0.082630	0.000000
io 55	0.256709	0.239647	0.168766	0.165857
io 97	0.013305	0.001418	0.025208	0.060620
lab 50017	0.050653	0.000000	0.000000	0.000000
lab 50019	-0.158086	-0.052493	-0.005761	0.150331
totalbal 1	-0.163953	-0.054532	-0.020873	0.034326
totalbal 16	0.001116	-0.027638	-0.055034	-0.056320
totalbal 19	0.010041	0.023816	0.007403	-0.003018
totalbal 20	-0.307291	-0.391029	-0.467305	-0.469405
totalbal 26	-0.595705	-0.639719	-0.604781	-0.536831
Set 9 Predictive Results				
Accuracy	83.92%	81.22%	79.17%	80.30%
PPV	87.80%	84.79%	81.65%	83.13%
Sensitivity	86.48%	88.33%	91.52%	92.63%
Specificity	79.58%	65.97%	47.87%	42.71%
NPV	77.58%	72.47%	69.01%	65.53%
AUC	83.03%	77.15%	69.70%	67.67%
Set 10 Parameters				
bias	0.6150488	0.856018	0.973612	1.148259

	48-hour model	24-hour model	12-hour model	6-hour model
chart 1162	-0.075004	-0.058842	0.000000	0.000000
chart 1531	-0.077247	-0.059779	-0.065061	-0.041495
chart 682	0.130835	0.199684	0.176202	0.000000
chart 779	0.060598	0.000000	0.180059	0.315992
chart 781	0.080529	0.041449	-0.053515	0.000000
chart 785	-0.050856	0.027466	0.000000	0.000000
chart 811	-0.583981	-0.391430	-0.499748	-0.283068
chart 818	-0.047807	0.000000	0.000000	0.000000
chart 828	-0.632393	-0.512623	0.000000	-0.327204
io 102	0.105973	0.125834	0.066088	0.052974
io 133	0.078028	0.068592	0.086727	0.000000
io 53	0.046452	0.000000	0.040153	0.028834
io 69	0.000000	-0.145370	-0.109129	-0.056514
io 97	0.012542	0.028264	0.039309	0.071315
lab 50017	0.062166	0.000000	0.000000	0.000000
lab 50019	-0.158595	-0.061223	-0.010076	0.149672
totalbal 1	-0.119621	-0.051519	0.005576	0.047070
totalbal 16	0.014249	-0.018354	-0.045066	-0.044854
totalbal 19	0.018959	0.035018	0.013853	0.005953
totalbal 2	-0.116124	0.000000	-0.106958	-0.052790
totalbal 20	-0.339871	-0.405354	-0.491820	-0.502403
totalbal 26	-0.402412	-0.515802	-0.430860	-0.399246
Set 10 Predictive Results				
Accuracy	84.01%	80.98%	78.98%	80.30%
PPV	87.79%	84.56%	81.56%	83.09%
Sensitivity	86.65%	88.22%	91.34%	92.71%
Specificity	79.50%	65.43%	47.64%	42.47%
NPV	77.79%	72.12%	68.44%	65.64%
AUC	83.08%	76.82%	69.49%	67.59%

As shown in the below examples, depending on the number of features identified using the above methods of the invention, the accuracy of predicting whether or not SIRS will occur can be predicted at 60% or greater, more preferably 70% or greater and most preferably 80% or greater. Predictions of patients likely to develop SIRS can lead to improved healthcare outcomes and reduced cost by appropriate monitoring and intervention.

Example 3: Models with Five Features Show a Range of Predictive Abilities

Machine learning was applied to the MIMIC II database as described above, using logistic regression on the 48-hour dataset, using feature sets of five features selected from the first 20 groups of **Table 4**. Machine learning models developed on a training dataset produced

a wide range of accuracies when applied to a testing dataset, from above 80% to below 70%, depending on the particular feature set used in the learning, as shown in **Table 6**.

Table 6. The parameters for 4 different predictive models trained and tested with the 48-hour dataset from MIMIC II are given together with the performance of those models.

	48-hour model
Set 1 Parameters	
bias	0.60467938
chart 811	-0.806772715
chart 818	-0.006220046
chart 1532	-0.401452681
lab 50030	-0.044147911
totalbal 26	-0.695661357
Set 1 Predictive Results	
Accuracy	83.67%
PPV	87.42%
Sensitivity	86.52%
Specificity	78.82%
NPV	77.47%
AUC	82.67%
Set 2 Parameters	
bias	0.490888658
lab 50030	-0.248727074
io 55	0.173756459
io 97	0.015815466
totalbal 2	-1.360023384
totalbal 16	0.035450753
Set 2 Predictive Results	
Accuracy	78.77%
PPV	78.52%
Sensitivity	91.24%
Specificity	57.56%
NPV	79.44%
AUC	74.40%
Set 3 Parameters	
bias	0.495140624
chart 818	-0.158001857
chart 1162	-0.778137982
lab 50019	-0.363315949
io 133	-0.017914369
totalbal 16	-0.137483415
Set 3 Predictive Results	
Accuracy	72.27%
PPV	72.50%
Sensitivity	90.17%
Specificity	41.83%

NPV	71.45%
AUC	66.00%
Set 4 Parameters	
bias	0.508688002
chart 682	-0.123597317
chart 1531	-0.338819848
lab 50019	-0.38430722
io 97	-0.020770998
totalbal 16	-0.157934522
Set 4 Predictive Results	
Accuracy	68.07%
PPV	68.47%
Sensitivity	91.37%
Specificity	28.44%
NPV	65.96%
AUC	59.91%

Example 4: Models with One or Two Features Also Show Predictive Abilities

Machine learning was applied to the MIMIC II database as described above, using logistic regression on the 48-hour dataset, using feature sets of one and two features selected from the first 20 groups of **Table 4**. Machine learning models developed on the training dataset produced useful accuracies when applied to the testing dataset, as shown in **Table 7**.

Table 7. The parameters for 4 different predictive models trained and tested with the 48-hour dataset from MIMIC II are given together with the performance of those models.

	48-hour model
Set 1 Parameters (2 features)	
bias	0.38570712
lab 50019	-0.353130872
io 102	-0.565988388
Set 1 Predictive Results	
Accuracy	71.46%
PPV	71.55%
Sensitivity	90.75%
Specificity	38.65%
NPV	71.07%
AUC	64.70%
Set 2 Parameters (2 features)	
bias	0.391267846
lab 50017	-0.136826972
io 97	-0.023012269
Set 2 Predictive Results	
Accuracy	68.32%

PPV	67.99%
Sensitivity	93.91%
Specificity	24.81%
NPV	70.54%
AUC	59.36%
Set 3 Parameters (1 feature)	
bias	0.394150338
lab 50019	-0.389236239
Set 3 Predictive Results	
Accuracy	66.86%
PPV	67.61%
Sensitivity	90.93%
Specificity	25.95%
NPV	62.71%
AUC	58.44%
Set 4 Parameters (1 feature)	
bias	0.393311091
chart 682	-0.304736694
Set 4 Predictive Results	
Accuracy	66.81%
PPV	66.65%
Sensitivity	94.66%
Specificity	19.44%
NPV	68.17%
AUC	57.05%

Example 5: Use of the Invention in a Hospital Setting

Using the invention, the probability of SIRS onset within a given time window for a given patient can be determined. The methods deployed here show methods for building predictive models for which patients will and which will not develop SIRS in a given time frame using a relatively small number of features (patient data measurements) pared down from the much larger number frequently available in a hospital database, such as the MIMIC II database. The models developed and shown here can be used directly to make predictions on hospital patients. One merely needs to acquire measurements of data for a particular patient corresponding to the features in the model, normalize them as shown here, use the model parameters (bias b and coefficients w_j), and apply the logistic regression formula to produce a probability of SIRS in the patient at the time point indicated by the model (6, 12, 24, or 48 hours). If the probability is greater than 50% (one-half), then SIRS is predicted; otherwise, it is not. As illustrated above, the probability can be used in a multitude of ways to assign a more fined grained classification of the likelihood of the patient developing SIRS.

The unexpectedly high predictive accuracy for SIRS of the methods of the invention has been shown in this application, for example, by the above accuracy and other determinations in the Predictive Results of Tables 2, 5, 6, and 7. The unexpectedly high predictive accuracy with relatively small sets of feature measurements has also been shown in this application. For example, using the features of Set 1 in **Table 6**, the method of the invention resulted in an 83.67% value for Accuracy regarding onset of SIRS in a 48-hour model. At its most general terms, this indicates that when the features of that Set 1 were applied to the above model based on the MIMIC II database, the predicted probability (yes or no) of the onset of SIRS at 48 hours resulted in 83.67% Accuracy. In other words, the Set 1 features were applied to the 80% of data designating as training data according to the above method to determine the probability of SIRS onset at 48 hours using those features, and the Accuracy result of 83.67% was determined against the 20% test data relative to those same features and whether or not SIRS occurred at 48 hours, as a person of ordinary skill in the art would appreciate.

Rather than use the precise models presented here directly, one can use the methods here to produce new models, using available hospital data (for example, historical or retrospective data from the previous few weeks, months, or years at the same or similar hospital or hospital system) and apply the methods of the invention to identify feature sets and models, and then to apply them as described here. The methods shown here can be used to prepare the data, select features, and carry out machine learning to produce models and evaluate the predictive ability of those models. The methods shown here can then be used to apply those models to make predictions on new patients using current measurements on those new patients.

For example, with regard to a patient who walks in the door of a hospital for assessment, the invention can be applied in the following manner relative to the MIMIC II database features. The patient's data can be obtained for the various primary, secondary, and additional features over the course of time and in the ordinary course of the patient's stay in the hospital. To the extent that the obtained measurements match any of the above models and their Parameter Sets, the method of the invention and the above models can be applied to the patient's features to determine the probability of the patient developing SIRS at 6, 12, 24 or 48 hours in the future. For example, if one has the measurement corresponding to lab 50019 (Set 3 from Table 7), one can make a prediction using that patient measurement, normalizing, and applying the coefficient and bias from the table to produce a probability of SIRS onset 48-hours into the future from when the measurement was taken. If one has the measurement corresponding to lab 50019 and that corresponding to io 102 (Set 1 from Table 7), then one can make a prediction using those two patient measurements, normalizing, and applying the

coefficients and bias from the table to produce a probability of SIRS onset 48-hours into the future from when the measurements were taken. From the results in Table 7, this two-feature model is expected to be more accurate than the one-feature model using only feature 50019 (Accuracy of 71.46% rather than 66.86%). If the model predicts such a probability of the onset of SIRS, the hospital can advantageously begin treating the patient for SIRS or sepsis before the onset of any symptoms, saving time and money as compared to waiting for the more dire situation where SIRS or sepsis symptoms have already occurred.

Alternatively, as features of the patient are ascertained during his or her stay at the hospital, new models can be created based on those features as described above (using the MIMIC II database) and tested for predictive accuracy in terms of the probability of SIRS onset in the patient. That is, if a patient's measurements correspond to a combination of features for which a model hasn't previously been trained, one can use methods described here to train such a model using historical (past) data with those features only. One can test those models on historical (past) testing set data as described here. One can assess the accuracy and other metrics quantifying the performance of the model on patients in the testing set as described here. Finally, one can then apply the model to the new patient or to new patients as described here. In this case, as in the others described here, treatment of the patient or patients for SIRS or sepsis can be advantageously initiated before the onset of SIRS or sepsis if the model predicts that it is probable the patient will have SIRS 6, 12, 24, or 48 hours in the future. Alternatively, a hospital could base the decision on whether to begin treatment for SIRS or sepsis in an asymptomatic patient based on the relative Predictive Results of the model (e.g., such treatment would begin in an asymptomatic patient for SIRS that the model of the invention predicts is probable for developing SIRS at a given time if the Predictive Results show an Accuracy of greater than 60% or greater than 70% or greater than 80%, etc.). For example, using a model with accuracy of 60–70% a given hospital may choose to only initiate treatment if the model predicts a 90% or greater probability of developing SIRS, but using a model with accuracy of 70–80% the same hospital may choose to initiate treatment if the model predicts an 80% or greater probability of developing SIRS, and using a model with accuracy of greater than 80% the same hospital may choose to initiate treatment if the model predicts a 70% or greater probability of developing SIRS.

On the other hand, a patient could walk in the door of a hospital that measures features in a manner that is different from that of the MIMIC II database (or some features are the same and one or more features are different in terms of units or a different measurement that is used to assess the same aspect of a patient or a different dose of the same or different medication is

used to treat the same aspect of a patient, etc.). First, the features that are different than the MIMIC II features can be mapped to the MIMIC II features by recognizing the similarity of what the measurement achieves (for example, different ways of measuring blood urea [group 2], glucose levels [group 3], cholesterol [group 16], and blood coagulability [chart 815 in group 18]). Then the above models or new models can be used in accordance with the invention to assess the probability of SIRS onset at a given time in the future, with advantageous early treatment being applied as set forth in the above paragraph. For example, simply developing new normalization parameters for new measurements using the method for how normalization was carried out here would allow new measurements to be incorporated into the models presented here. Alternatively, if there is an existing database for the particular hospital that uses features other than MIMIC II features (or a mixture of MIMIC II features and other features), new models can be prepared in accordance with the methods of the invention to select primary, secondary, and additional features from that database that can be used to predict the probability of SIRS onset in a patient in accordance with the methods of the invention described herein. As described here, features would be eliminated and selected, data normalized, and models built and tested using the methods disclosed in this application. The patient's data then can be obtained for these various primary, secondary, and additional features over the course of time and in the ordinary course of the patient's stay in the hospital. These new models prepared using the hospital's database can be applied to the patient's features to determine the probability of the patient developing SIRS at 6, 12, 24, or 48 hours in the future. Patient measurements can be normalized, inserted into the model, and the model would then make a prediction regarding the probability of the onset of SIRS. Alternatively, as features of the patient are ascertained (measured) during his or her stay at the hospital, new models can be created based on those features in accordance with the methods described above (using the hospital's database) and tested for predictive accuracy in terms of the probability of SIRS onset in the patient using historical (past) patients at the same or similar hospital or hospital system, as described above. New measurements for the patient can be used in these new models to predict the probability of the onset of SIRS in the new patient. In either case, treatment of the patient for SIRS can be advantageously initiated before the onset of SIRS if the model predicts that it is probable the patient will have SIRS 6, 12, 24, or 48 hours in the future. Alternatively, a hospital could base the decision on whether to begin treatment for SIRS in an asymptomatic patient based on the relative Predictive Results of the model (e.g., such treatment would begin in an asymptomatic patient for SIRS that the model of the invention predicts is probable for developing SIRS at a given time if the Predictive Results show an Accuracy of greater than 60% or greater than 70%

or greater than 80%, etc.). For example, using a model with accuracy of 60–70%, a given hospital may choose to only initiate treatment if the model predicts a 90% or greater probability of developing SIRS, but using a model with accuracy of 70–80%, the same hospital may choose to initiate treatment if the model predicts an 80% or greater probability of developing SIRS, and using a model with accuracy of greater than 80%, the same hospital may choose to initiate treatment if the model predicts a 70% or greater probability of developing SIRS.

In another example embodiment of the invention, a hospital, medical center, or health care system maintains multiple models simultaneously. The measurements for a patient can be input into multiple models to obtain multiple probabilities of the onset of SIRS at the same or different times in the future. These different predictive probabilities can be combined to develop an aggregate likelihood or probability of developing SIRS and an action plan can be developed accordingly. For example, the different models could vote as to whether they expected SIRS onset within a given timeframe, and the aggregate prediction could be made based on the outcome of this voting scheme. The voting can be unweighted (each model receives an equal vote), or weighted based on the accuracy or other quantitative metric of the predictive abilities of each model (with more accurate or higher quality models casting a higher proportional vote).

In yet another example embodiment of the invention, one can use multiple models and base a prediction on the first one for which a sufficient number of measurements have been obtained for the current patient. In another aspect of the invention, in any of the embodiments described, the parameters for a model can be re-computed (updated) using additional data from the greater number of historical patients available as time progresses. For example, every year, every month, every week, or every day, an updated database of historical (past) patients can be used to retrain the set of models in active use by creating a training and testing dataset from the available past data, training the models on the training data, and testing them to provide quantitative assessment on the testing data as described here.

An example embodiment of the present invention is directed to one or more processors, which can be implemented using any conventional processing circuit and device or combination thereof, e.g., a Central Processing Unit (CPU) of a Personal Computer (PC) or other workstation processor, to execute code provided, e.g., on a hardware computer-readable medium including any conventional memory device, to perform any of the methods described herein, alone or in combination. For example, in an example embodiment, the circuitry interfaces with a patient population database, obtaining therefrom data, and executes an algorithm by which the circuitry generates prediction models, as described above. In an

example embodiment, the circuitry generates the models in the form of further executables processable by the circuitry (or other circuitry) to predict onset of a disease (or diagnose a disease) based on respective datasets of a respective patient. In an alternative example embodiment, the algorithms are programmed in hardwired fashion in the circuitry, e.g., in the form of an application specific integrated circuit (ASIC). The one or more processors can be embodied in a server or user terminal or combination thereof. The user terminal can be embodied, for example, as a desktop, laptop, hand-held device, Personal Digital Assistant (PDA), television set-top Internet appliance, mobile telephone, smart phone, etc., or as a combination of one or more thereof. The memory device can include any conventional permanent and/or temporary memory circuits or combination thereof, a non-exhaustive list of which includes Random Access Memory (RAM), Read Only Memory (ROM), Compact Disks (CD), Digital Versatile Disk (DVD), and magnetic tape.

An example embodiment of the present invention is directed to one or more hardware computer-readable media, e.g., as described above, on which are stored instructions executable by a processor to perform the methods described herein.

An example embodiment of the present invention is directed to the described methods being executed by circuitry, such as that described above.

An example embodiment of the present invention is directed to a method, e.g., of a hardware component or machine, of transmitting instructions executable by a processor to perform the methods described herein.

DETAILED DESCRIPTION OF FIGURES

Figure 1 illustrates an embodiment of the system utilized in the present disclosure. For example, as depicted in Figure 1, system 100 includes a plurality of user terminals 102: laptops 102a and 102e, desktops 102b and 102f, hand-held devices 102c and 102g (e.g., smart phones, tablets, etc.), and other user terminals 102d and 102an. Further, in an embodiment, the other user terminals 102d and 102an can be any of a television set-top Internet appliance, mobile telephone, PDA, etc., or as a combination of one or more thereof. The system 100 also includes a communication network 104 and one or more processors 106. In an embodiment, the user terminals 102 interact with the one or more processors 106 via the communication network 104. In an embodiment, as discussed above, the processor 106 can be implemented using any conventional processing circuit and device or combination thereof, e.g., a Central Processing Unit (CPU) of a Personal Computer (PC) or other workstation processor or server, to execute code provided, e.g., on a hardware computer-readable medium including any conventional memory device, to perform any of the methods described herein, alone or in combination. For

example, computational machine learning models running on one or more processors 106 can send predicted SIRS probabilities (or other predictions) to selected user terminals 102, 102a, 102b, 102c, etc. through the communication network 104. Users may choose to add notes, observations, or actions taken that are to be added to the patient data record by sending them through user terminals 102, 102a, 102b, 102c, etc. through the communication network 104 to one or more processors 106.

The above description is intended to be illustrative, and not restrictive. Those skilled in the art can appreciate from the foregoing description that the present invention may be implemented in a variety of forms, and that the various embodiments may be implemented alone or in combination. Therefore, while the embodiments of the present invention have been described in connection with particular examples thereof, the true scope of the embodiments and/or methods of the present invention should not be so limited since other modifications will become apparent to the skilled practitioner upon a study of the specification and following claims.

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WHAT IS CLAIMED IS:

Claim 1: A system for disease prediction, the system comprising:

processing circuitry including an interface, wherein the processing circuitry is configured to:

receive, via the interface, a dataset including data of a patient population, the data including for each of a plurality of patients of the patient population, values for a plurality of features and a diagnosis value of a diagnosis feature indicating whether a disease has been diagnosed;

based on correlations between the values, select from the dataset a plurality of subsets of the features; and

for each of at least one of the subsets:

execute a machine learning process with the respective subset and the diagnosis feature as input parameters, the execution generating a respective prediction model; and

output the respective prediction model.

Claim 2: The system of Claim 1, wherein the selection of the plurality of subsets includes, for each of the plurality of subsets, (a) selecting a respective first one of the plurality of features as a primary feature based on a correlation of the respective first feature with the diagnosis feature, and (b) selecting a respective set of second ones of the plurality of features as secondary features based on a respective correlation of each of the respective second features with the respective first feature of the respective subset.

Claim 3: The system of Claim 2, wherein, for each of the primary features, a feature is selected as a secondary feature of the respective primary feature conditional upon that the feature has a threshold level of correlation with the respective primary feature.

Claim 4: The system of Claim 3, wherein the threshold level of correlation is 60% correlation.

Claim 5: The system of Claim 2, wherein:

the selection of the plurality of subsets is performed iteratively, a respective one of the plurality of subsets being selected in each iteration; and

for each of the iterations, the subset selected in the respective iteration is removed from the dataset so that none of the features of the respective subset is selectable as a primary feature in any of the subsequent iterations and so that none of the features of the respective subset is selectable as a secondary feature in any of the subsequent iterations.

Claim 6: The system of Claim 5, wherein:

the iterative selection includes, after each of the iterations:

applying the machine learning to a combination of all remaining features of the dataset; and

based on the application, determining whether the disease is predictable based on a prediction model whose parameters are values of the remaining features of the dataset; and

the iterative selection is ended in response to a negative result of the determination.

Claim 7: The system of Claim 5, wherein:

the processing circuitry is further configured to divide the dataset into a training dataset and a testing dataset;

the machine learning process is executed based only on values of the training dataset; and

for each of the generated prediction models, the processing circuitry is configured to apply the generated prediction model to data of the testing dataset to determine a respective degree of prediction accuracy of the respective prediction model.

Claim 8: The system of Claim 7, wherein the outputting is only of those of the generated prediction models for which the determined degree of prediction accuracy satisfies a predefined threshold.

Claim 9: The system of Claim 5, wherein, in each iteration, whichever of the features remaining in the dataset has the strongest correlation with the diagnosis feature is selected as the primary feature of the respective subset.

Claim 10: The system of Claim 9, wherein the processor is configured to, prior to the execution of the iterative selection:

for each of the features of the dataset, determine a distribution of values of the feature between entries that include a diagnosis value indicating that the disease has been diagnosed

and entries that include a diagnosis value indicating that the disease has not been diagnosed; and

remove from the dataset all those entries whose distributions differ by less than a threshold amount, the iterative selection being performed only on those of the features remaining in the dataset after the removal.

Claim 11: The system of Claim 5, wherein:

the dataset includes a plurality of datasets, each of the datasets corresponding to a respective onset time period, the diagnosis values of each of the datasets indicating whether the disease had been diagnosed within the respective time period to which the respective dataset corresponds;

the output prediction models include one or more prediction models for each of the onset time periods; and

each of the output prediction models, when executed, is configured to output a probability of onset of the disease within the onset time period to which the respective prediction model corresponds.

Claim 12: The system of Claim 11, wherein:

the iterative selection results in selection of a subset for one of the onset time periods, which is not selected for another one of the onset time periods; and

a subset selected by the iterative selection for one of the onset time periods and not for another one of the onset time periods is applied as input even to the machine learning process whose output prediction model is associated with the onset time period for which the subset was not selected.

Claim 13: The system of Claim 11, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS) and the onset time periods are 6, 12, 24, and 48 hours.

Claim 14: The system of Claim 5, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS).

Claim 15: The system of Claim 14, wherein the prediction model is a regression model.

Claim 16: The system of Claim 15, wherein:

the model is $P(SIRS|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(SIRS|\text{patient\_data}_i)$ is a probability that a particular patient i, to which patient data represented by a vector patient_data_i corresponds, will develop SIRS;

b is a model bias parameter;

num_features is the number of features in the respective subset of the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the subset to which the model corresponds.

Claim 17: A computer-implemented method for disease prediction, the method comprising:

accessing, by processing circuitry, a dataset of a database, the dataset including data of a patient population, the data including for each of a plurality of patients of the patient population, values for a plurality of features and a diagnosis value of a diagnosis feature indicating whether a disease has been diagnosed;

based on correlations between the values, selecting, by the processing circuitry and from the dataset, a plurality of subsets of the features; and

for each of at least one of the subsets:

executing, by the processing circuitry, a machine learning process with the respective subset and the diagnosis feature as input parameters, the execution generating a respective prediction model; and

outputting, by the processing circuitry, the respective prediction model.

Claim 18: The method of Claim 17, wherein the selection of the plurality of subsets includes, for each of the plurality of subsets, (a) selecting a respective first one of the plurality of features as a primary feature based on a correlation of the respective first feature with the diagnosis feature, and (b) selecting a respective set of second ones of the plurality of features as secondary features based on a respective correlation of each of the respective second features with the respective first feature of the respective subset.

Claim 19: The method of Claim 18, wherein, for each of the primary features, a feature is selected as a secondary feature of the respective primary feature conditional upon that the feature has a threshold level of correlation with the respective primary feature.

Claim 20: The method of Claim 19, wherein the threshold level of correlation is 60% correlation.

Claim 21: The method of Claim 18, wherein:

the selection of the plurality of subsets is performed iteratively, a respective one of the plurality of subsets being selected in each iteration; and

for each of the iterations, the subset selected in the respective iteration is removed from the dataset so that none of the features of the respective subset is selectable as a primary feature in any of the subsequent iterations and so that none of the features of the respective subset is selectable as a secondary feature in any of the subsequent iterations.

Claim 22: The method of Claim 21, wherein:

the iterative selection includes, after each of the iterations:

applying the machine learning to a combination of all remaining features of the dataset; and

based on the application, determining whether the disease is predictable based on a prediction model whose parameters are values of the remaining features of the dataset; and

the iterative selection is ended in response to a negative result of the determination.

Claim 23: The method of Claim 21, further comprising:

dividing the dataset into a training dataset and a testing dataset, wherein the machine learning process is executed based only on values of the training dataset; and

for each of the generated prediction models, applying the generated prediction model to data of the testing dataset to determine a respective degree of prediction accuracy of the respective prediction model.

Claim 24: The method of Claim 23, wherein the outputting is only of those of the generated prediction models for which the determined degree of prediction accuracy satisfies a predefined threshold.

Claim 25: The method of Claim 21, wherein, in each iteration, whichever of the features remaining in the dataset has the strongest correlation with the diagnosis feature is selected as the primary feature of the respective subset.

Claim 26: The method of Claim 25, further comprising, prior to the execution of the iterative selection:

for each of the features of the dataset, determining a distribution of values of the feature between entries that include a diagnosis value indicating that the disease has been diagnosed and entries that include a diagnosis value indicating that the disease has not been diagnosed; and

removing from the dataset all those entries whose distributions differ by less than a threshold amount, the iterative selection being performed only on those of the features remaining in the dataset after the removal.

Claim 27: The method of Claim 21, wherein:

the dataset includes a plurality of datasets, each of the datasets corresponding to a respective onset time period, the diagnosis values of each of the datasets indicating whether the disease had been diagnosed within the respective time period to which the respective dataset corresponds;

the output prediction models include one or more prediction models for each of the onset time periods; and

each of the output prediction models, when executed, is configured to output a probability of onset of the disease within the onset time period to which the respective prediction model corresponds.

Claim 28: The method of Claim 27, wherein:

the iterative selection results in selection of a subset for one of the onset time periods, which is not selected for another one of the onset time periods; and

a subset selected by the iterative selection for one of the onset time periods and not for another one of the onset time periods is applied as input even to the machine learning process whose output prediction model is associated with the onset time period for which the subset was not selected.

Claim 29: The method of Claim 27, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS) and the onset time periods are 6, 12, 24, and 48 hours.

Claim 30: The method of Claim 21, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS).

Claim 31: The method of Claim 30, wherein the prediction model is a regression model.

Claim 32: The method of Claim 31, wherein:

the model is $P(SIRS|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(SIRS|\text{patient\_data}_i)$ is a probability that a particular patient i, to which patient data represented by a vector patient_data_i corresponds, will develop SIRS;

b is a model bias parameter;

num_features is the number of features in the respective subset of the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the subset to which the model corresponds.

Claim 33: A non-transitory computer-readable medium on which are stored instructions that are executable by a processor and that, when executed by the processor, cause the processor to perform a method for disease prediction, the method comprising:

accessing a dataset of a database, the dataset including data of a patient population, the data including for each of a plurality of patients of the patient population, values for a plurality of features and a diagnosis value of a diagnosis feature indicating whether a disease has been diagnosed;

based on correlations between the values, selecting from the dataset a plurality of subsets of the features; and

for each of at least one of the subsets:

executing a machine learning process with the respective subset and the diagnosis feature as input parameters, the execution generating a respective prediction model; and

outputting the respective prediction model.

Claim 34: The non-transitory computer-readable medium of Claim 33, wherein the selection of the plurality of subsets includes, for each of the plurality of subsets, (a) selecting a respective first one of the plurality of features as a primary feature based on a correlation of the respective first feature with the diagnosis feature, and (b) selecting a respective set of second ones of the plurality of features as secondary features based on a respective correlation of each of the respective second features with the respective first feature of the respective subset.

Claim 35: The non-transitory computer-readable medium of Claim 34, wherein, for each of the primary features, a feature is selected as a secondary feature of the respective primary feature conditional upon that the feature has a threshold level of correlation with the respective primary feature.

Claim 36: The non-transitory computer-readable medium of Claim 35, wherein the threshold level of correlation is 60% correlation.

Claim 37: The non-transitory computer-readable medium of Claim 34, wherein:

the selection of the plurality of subsets is performed iteratively, a respective one of the plurality of subsets being selected in each iteration; and

for each of the iterations, the subset selected in the respective iteration is removed from the dataset so that none of the features of the respective subset is selectable as a primary feature in any of the subsequent iterations and so that none of the features of the respective subset is selectable as a secondary feature in any of the subsequent iterations.

Claim 38: The non-transitory computer-readable medium of Claim 36, wherein:

the iterative selection includes, after each of the iterations:

applying the machine learning to a combination of all remaining features of the dataset; and

based on the application, determining whether the disease is predictable based on a prediction model whose parameters are values of the remaining features of the dataset; and

the iterative selection is ended in response to a negative result of the determination.

Claim 39: The non-transitory computer-readable medium of Claim 36, wherein the method further comprises:

dividing the dataset into a training dataset and a testing dataset, wherein the machine learning process is executed based only on values of the training dataset; and

for each of the generated prediction models, applying the generated prediction model to data of the testing dataset to determine a respective degree of prediction accuracy of the respective prediction model.

Claim 40: The non-transitory computer-readable medium of Claim 39, wherein the outputting is only of those of the generated prediction models for which the determined degree of prediction accuracy satisfies a predefined threshold.

Claim 41: The non-transitory computer-readable medium of Claim 36, wherein, in each iteration, whichever of the features remaining in the dataset has the strongest correlation with the diagnosis feature is selected as the primary feature of the respective subset.

Claim 42: The non-transitory computer-readable medium of Claim 41, wherein the method further comprises, prior to the execution of the iterative selection:

for each of the features of the dataset, determining a distribution of values of the feature between entries that include a diagnosis value indicating that the disease has been diagnosed and entries that include a diagnosis value indicating that the disease has not been diagnosed; and

removing from the dataset all those entries whose distributions differ by less than a threshold amount, the iterative selection being performed only on those of the features remaining in the dataset after the removal.

Claim 43: The non-transitory computer-readable medium of Claim 36, wherein:

the dataset includes a plurality of datasets, each of the datasets corresponding to a respective onset time period, the diagnosis values of each of the datasets indicating whether the disease had been diagnosed within the respective time period to which the respective dataset corresponds;

the output prediction models include one or more prediction models for each of the onset time periods; and

each of the output prediction models, when executed, is configured to output a probability of onset of the disease within the onset time period to which the respective prediction model corresponds.

Claim 44: The non-transitory computer-readable medium of Claim 43, wherein:

the iterative selection results in selection of a subset for one of the onset time periods, which is not selected for another one of the onset time periods; and

a subset selected by the iterative selection for one of the onset time periods and not for another one of the onset time periods is applied as input even to the machine learning process

whose output prediction model is associated with the onset time period for which the subset was not selected.

Claim 45: The non-transitory computer-readable medium of Claim 43, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS) and the onset time periods are 6, 12, 24, and 48 hours.

Claim 46: The non-transitory computer-readable medium of Claim 36, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS).

Claim 47: The non-transitory computer-readable medium of Claim 46, wherein the prediction model is a regression model.

Claim 48: The non-transitory computer-readable medium of Claim 47, wherein:

the model is $P(SIRS|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(SIRS|\text{patient\_data}_i)$ is a probability that a particular patient i, to which patient data represented by a vector patient_data_i corresponds, will develop SIRS;

b is a model bias parameter;

num_features is the number of features in the respective subset of the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the subset to which the model corresponds.

Claim 49: A system for disease prediction, the system comprising:

processing circuitry including at least one interface, wherein the processing circuitry is configured to:

receive via the at least one interface a set of data associated with a particular patient;

based on the received set of data, select one of a plurality of prediction models;

execute the selected prediction model by populating parameters of the prediction model with values from the received set of data; and

output via the at least one interface a probability of the particular patient developing the disease within a particular time frame.

Claim 50: The system of Claim 49, wherein different ones of the plurality of prediction models correspond to different groups of features, and the selection is from only those of the prediction models for each of the features of the groups of features of which the set of data includes a respective value.

Claim 51: The system of Claim 49, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS).

Claim 52: The system of Claim 51, wherein:

the selected model is $P(SIRS|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(SIRS|\text{patient\_data}_i)$ is a probability that the particular patient i, to which the set of data represented by a vector patient_data_i corresponds, will develop SIRS;

b is a model bias parameter;

num_features is the number of features in the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the features of the model.

Claim 53: The system of Claim 49, wherein:

the selected model is

$P(DISEASE|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(DISEASE|\text{patient\_data}_i)$ is a probability that the particular patient i, to which the set of data represented by a vector patient_data_i corresponds, will develop the disease;

b is a model bias parameter;

num_features is the number of features in the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the features of the model.

Claim 54: A computer-implemented method for disease prediction, the method comprising:

receiving, by processing circuitry, a set of data associated with a particular patient;

based on the received set of data, selecting, by the processing circuitry, one of a plurality of prediction models;

executing, by the processing circuitry, the selected prediction model by populating parameters of the prediction model with values from the received set of data; and

outputting, by the processing circuitry and via an output device, a probability of the particular patient developing the disease within a particular time frame.

Claim 55: The method of Claim 54, wherein different ones of the plurality of prediction models correspond to different groups of features, and the selection is from only those of the prediction models for each of the features of the groups of features of which the set of data includes a respective value.

Claim 56: The method of Claim 54, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS).

Claim 57: The method of Claim 56, wherein:

the selected model is $P(SIRS|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(SIRS|\text{patient\_data}_i)$ is a probability that the particular patient i, to which the set of data represented by a vector patient_data_i corresponds, will develop SIRS;

b is a model bias parameter;

num_features is the number of features in the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the features of the model.

Claim 58: The method of Claim 54, wherein:

the selected model is

$P(DISEASE|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(DISEASE|\text{patient\_data}_i)$ is a probability that the particular patient i, to which the set of data represented by a vector patient_data_i corresponds, will develop the disease;

b is a model bias parameter;

num_features is the number of features in the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the features of the model.

Claim 59: A non-transitory computer-readable medium on which are stored instructions that are executable by a processor and that, when executed by the processor, cause the processor to perform a method for disease prediction, the method comprising:

receiving a set of data associated with a particular patient;

based on the received set of data, selecting one of a plurality of prediction models;

executing the selected prediction model by populating parameters of the prediction model with values from the received set of data; and

outputting, via an output device, a probability of the particular patient developing the disease within a particular time frame.

Claim 60: The non-transitory computer-readable medium of Claim 59, wherein different ones of the plurality of prediction models correspond to different groups of features, and the selection is from only those of the prediction models for each of the features of the groups of features of which the set of data includes a respective value.

Claim 61: The non-transitory computer-readable medium of Claim 59, wherein the disease is Systemic Inflammatory Response Syndrome (SIRS).

Claim 62: The non-transitory computer-readable medium of Claim 61, wherein:

the selected model is $P(SIRS|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(SIRS|\text{patient\_data}_i)$ is a probability that the particular patient i, to which the set of data represented by a vector patient_data_i corresponds, will develop SIRS;

b is a model bias parameter;

num_features is the number of features in the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the features of the model.

Claim 63: The non-transitory computer-readable medium of Claim 59, wherein:

the selected model is

$P(DISEASE|\text{patient\_data}_i) = \frac{1}{1+\exp\left(-b-\sum_{j=1}^{\text{num\_features}} w_j \times \text{patient\_data}_{i,j}\right)}$;

$P(DISEASE|\text{patient\_data}_i)$ is a probability that the particular patient i, to which the set of data represented by a vector patient_data_i corresponds, will develop the disease;

b is a model bias parameter;

num_features is the number of features in the model, indexed by j; and

w_j is a model coefficient for a respective one of the features j of the features of the model.

Claim 64: A system for predicting Systemic Inflammatory Response Syndrome (SIRS), the system comprising:

processing circuitry including at least one interface, wherein the processing circuitry is configured to:

receive via the at least one interface a set of data associated with a particular patient;

select a prediction model;

execute the selected prediction model by populating parameters of the prediction model with values from the received set of data; and

output via the at least one interface a probability of the particular patient developing SIRS within a particular time frame.

Claim 65: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are Lactic Acid (0.5-2.0) and Lactic Acid.

Claim 66: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are Blood Urea Nitrogen (BUN) and BUN (6-20).

Claim 67: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are Platelets, Glucose (70-105), and Glucose.

Claim 68: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are PO/Gastric In Total and PO Intake.

Claim 69: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are PO2 and Arterial PaO2.

Claim 70: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are Urine Out Total, 24-hr Total Out, IV Infusion In Total, and Urine Out Foley.

Claim 71: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are INR (2–4 ref. range), Magnesium (1.6–2.6), Magnesium, and free Ca.

Claim 72: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are Fibrinogen, GCS Total Glasgow Coma Scale, SAPS-I Simplified Acute Physiology Score, Overall SOFA (Sequen. Organ Failure) Score, Heart Rate, TCPCV Insp. Time Ventilation, Alk. Phosphate, D-Dimer (0-500), Gentamycin/Random, Phenobarbital, Vancomycin/Trough, Braden Score, Stool Out Fecal Bag, Urine Out Void, Dilaudid, and Ultrafiltrate Total.

Claim 73: The system of Claim 64, wherein only IV Nutrition Total is a parameter of the prediction model that is populated by the set of data.

Claim 74: The system of Claim 64, wherein only Tidal Volume (Observ.) Lung Vol. Displac. is a parameter of the prediction model that is populated by the set of data.

Claim 75: The system of Claim 64, wherein only CPK/MB Blood Test is a parameter of the prediction model that is populated by the set of data.

Claim 76: The system of Claim 64, wherein only Cerebral Drain L Ventricular Drain is a parameter of the prediction model that is populated by the set of data.

Claim 77: The system of Claim 64, wherein only positive end respiratory pressure (PEEP) is a parameter of the prediction model that is populated by the set of data.

Claim 78: The system of Claim 64, wherein only 24-hr Total In is a parameter of the prediction model that is populated by the set of data.

Claim 79: The system of Claim 64, wherein only Gastric Out Total is a parameter of the prediction model that is populated by the set of data.

Claim 80: The system of Claim 64, wherein only D5W 250.0 ml + 100 mcg/kg/min Nitroglycerine-k is a parameter of the prediction model that is populated by the set of data.

Claim 81: The system of Claim 64, wherein only Tidal Volume (Set) is a parameter of the prediction model that is populated by the set of data.

Claim 82: The system of Claim 64, wherein only Cholesterol (< 200) is a parameter of the prediction model that is populated by the set of data.

Claim 83: The system of Claim 64, wherein only Fingerstick Glucose is a parameter of the prediction model that is populated by the set of data.

Claim 84: The system of Claim 64, wherein only 0.9% Normal Saline 1000 ml is a parameter of the prediction model that is populated by the set of data.

Claim 85: The system of Claim 64, wherein only Total Hourly Output is a parameter of the prediction model that is populated by the set of data.

Claim 86: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1528, chart 1531, chart 198, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 87: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 198, chart 20001, chart 682, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 88: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 20001, chart 20009, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 89: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162,

chart 1529, chart 1531, chart 20009, chart 211, chart 682, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, and totalbal 26.

Claim 90: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 211, chart 671, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 91: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 671, chart 682, chart 773, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 92: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 773, chart 779, chart 781, chart 785, chart 793, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 93: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 793, chart 809, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 94: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 809, chart 811, chart 818, chart 826, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 95: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 53, io 69, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 96: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 811, chart 818, chart 1532, lab 50030, and totalbal 26.

Claim 97: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50030, io 55, io 97, totalbal 2, and totalbal 16.

Claim 98: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 818, chart 1162, lab 50019, io 133, and totalbal 16.

Claim 99: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 682, chart 1531, lab 50019, io 97, and totalbal 16.

Claim 100: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50019 and io 102.

Claim 101: The system of Claim 64, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50017 and io 97.

Claim 102: The system of Claim 64, wherein only lab 50019, as defined in MIMIC II database, is a parameter of the prediction model that is populated by the set of data.

Claim 103: The system of Claim 64, wherein only lab chart 682, as defined in MIMIC II database, is a parameter of the prediction model that is populated by the set of data.

Claim 104: The system of Claim 64, wherein only a single parameter of the prediction model is populated by the data set.

Claim 105: The system of Claim 64, wherein at least one of the parameters is a measurement related to a blood glucose level.

Claim 106: The system of Claim 64, wherein at least one of the parameters is a measurement related to oxygen saturation in blood.

Claim 107: A computer-implemented method for predicting Systemic Inflammatory Response Syndrome (SIRS), the method comprising:

receiving, by processing circuitry, a set of data associated with a particular patient;

selecting, by the processing circuitry, a prediction model;

executing, by the processing circuitry, the selected prediction model by populating parameters of the prediction model with values from the received set of data; and

outputting, by the processing circuitry and via an output device, a probability of the particular patient developing SIRS within a particular time frame.

Claim 108: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are Lactic Acid (0.5-2.0) and Lactic Acid.

Claim 109: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are Blood Urea Nitrogen (BUN) and BUN (6-20).

Claim 110: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are Platelets, Glucose (70-105), and Glucose.

Claim 111: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are PO/Gastric In Total and PO Intake.

Claim 112: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are PO2 and Arterial PaO2.

Claim 113: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are Urine Out Total, 24-hr Total Out, IV Infusion In Total, and Urine Out Foley.

Claim 114: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are INR (2–4 ref. range), Magnesium (1.6–2.6), Magnesium, and free Ca.

Claim 115: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are Fibrinogen, GCS Total Glasgow Coma Scale, SAPS-I Simplified Acute Physiology Score, Overall SOFA (Sequen. Organ Failure) Score, Heart Rate, TCPCV Insp. Time Ventilation, Alk. Phosphate, D-Dimer (0-500), Gentamycin/Random, Phenobarbital, Vancomycin/Trough, Braden Score, Stool Out Fecal Bag, Urine Out Void, Dilaudid, and Ultrafiltrate Total.

Claim 116: The method of Claim 107, wherein only IV Nutrition Total is a parameter of the prediction model that is populated by the set of data.

Claim 117: The method of Claim 107, wherein only Tidal Volume (Observ.) Lung Vol. Displac. is a parameter of the prediction model that is populated by the set of data.

Claim 118: The method of Claim 107, wherein only CPK/MB Blood Test is a parameter of the prediction model that is populated by the set of data.

Claim 119: The method of Claim 107, wherein only Cerebral Drain L Ventricular Drain is a parameter of the prediction model that is populated by the set of data.

Claim 120: The method of Claim 107, wherein only positive end respiratory pressure (PEEP) is a parameter of the prediction model that is populated by the set of data.

Claim 121: The method of Claim 107, wherein only 24-hr Total In is a parameter of the prediction model that is populated by the set of data.

Claim 122: The method of Claim 107, wherein only Gastric Out Total is a parameter of the prediction model that is populated by the set of data.

Claim 123: The method of Claim 107, wherein only D5W 250.0 ml + 100 mcg/kg/min Nitroglycerine-k is a parameter of the prediction model that is populated by the set of data.

Claim 124: The method of Claim 107, wherein only Tidal Volume (Set) is a parameter of the prediction model that is populated by the set of data.

Claim 125: The method of Claim 107, wherein only Cholesterol (< 200) is a parameter of the prediction model that is populated by the set of data.

Claim 126: The method of Claim 107, wherein only Fingerstick Glucose is a parameter of the prediction model that is populated by the set of data.

Claim 127: The method of Claim 107, wherein only 0.9% Normal Saline 1000 ml is a parameter of the prediction model that is populated by the set of data.

Claim 128: The method of Claim 107, wherein only Total Hourly Output is a parameter of the prediction model that is populated by the set of data.

Claim 129: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1528, chart 1531, chart 198, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 130: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 198, chart 20001, chart 682, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 131: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 20001, chart 20009, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 132: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 20009, chart 211, chart 682, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, and totalbal 26.

Claim 133: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 211, chart 671, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 134: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 671, chart 682, chart 773, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 135: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 773, chart 779, chart 781, chart 785, chart 793, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 136: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 793, chart 809, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 137: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 809, chart 811, chart 818, chart 826, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 138: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 53, io 69, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 139: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 811, chart 818, chart 1532, lab 50030, and totalbal 26.

Claim 140: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50030, io 55, io 97, totalbal 2, and totalbal 16.

Claim 141: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 818, chart 1162, lab 50019, io 133, and totalbal 16.

Claim 142: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 682, chart 1531, lab 50019, io 97, and totalbal 16.

Claim 143: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50019 and io 102.

Claim 144: The method of Claim 107, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50017 and io 97.

Claim 145: The method of Claim 107, wherein only lab 50019, as defined in MIMIC II database, is a parameter of the prediction model that is populated by the set of data.

Claim 146: The method of Claim 107, wherein only lab chart 682, as defined in MIMIC II database, is a parameter of the prediction model that is populated by the set of data.

Claim 147: The method of Claim 107, wherein only a single parameter of the prediction model is populated by the data set.

Claim 148: The method of Claim 107, wherein at least one of the parameters is a measurement related to a blood glucose level.

Claim 149: The method of Claim 107, wherein at least one of the parameters is a measurement related to oxygen saturation in blood.

Claim 150: A non-transitory computer-readable medium on which are stored instructions that are executable by a processor and that, when executed by the processor, cause the processor to perform a method for predicting Systemic Inflammatory Response Syndrome (SIRS), the method comprising:

receiving a set of data associated with a particular patient;

selecting a prediction model;

executing the selected prediction model by populating parameters of the prediction model with values from the received set of data; and

outputting via an output device a probability of the particular patient developing SIRS within a particular time frame.

Claim 151: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are Lactic Acid (0.5-2.0) and Lactic Acid.

Claim 152: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are Blood Urea Nitrogen (BUN) and BUN (6-20).

Claim 153: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are Platelets, Glucose (70-105), and Glucose.

Claim 154: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are PO/Gastric In Total and PO Intake.

Claim 155: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are PO2 and Arterial PaO2.

Claim 156: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are Urine Out Total, 24-hr Total Out, IV Infusion In Total, and Urine Out Foley.

Claim 157: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are INR (2–4 ref. range), Magnesium (1.6–2.6), Magnesium, and free Ca.

Claim 158: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are Fibrinogen, GCS Total Glasgow Coma Scale, SAPS-I Simplified Acute Physiology Score, Overall SOFA (Sequen. Organ Failure) Score, Heart Rate, TCPCV Insp. Time Ventilation, Alk. Phosphate, D-Dimer (0-500), Gentamycin/Random, Phenobarbital, Vancomycin/Trough, Braden Score, Stool Out Fecal Bag, Urine Out Void, Dilaudid, and Ultrafiltrate Total.

Claim 159: The non-transitory computer-readable medium of Claim 150, wherein only IV Nutrition Total is a parameter of the prediction model that is populated by the set of data.

Claim 160: The non-transitory computer-readable medium of Claim 150, wherein only Tidal Volume (Observ.) Lung Vol. Displac. is a parameter of the prediction model that is populated by the set of data.

Claim 161: The non-transitory computer-readable medium of Claim 150, wherein only CPK/MB Blood Test is a parameter of the prediction model that is populated by the set of data.

Claim 162: The non-transitory computer-readable medium of Claim 150, wherein only Cerebral Drain L Ventricular Drain is a parameter of the prediction model that is populated by the set of data.

Claim 163: The non-transitory computer-readable medium of Claim 150, wherein only positive end respiratory pressure (PEEP) is a parameter of the prediction model that is populated by the set of data.

Claim 164: The non-transitory computer-readable medium of Claim 150, wherein only 24-hr Total In is a parameter of the prediction model that is populated by the set of data.

Claim 165: The non-transitory computer-readable medium of Claim 150, wherein only Gastric Out Total is a parameter of the prediction model that is populated by the set of data.

Claim 166: The non-transitory computer-readable medium of Claim 150, wherein only D5W 250.0 ml + 100 mcg/kg/min Nitroglycerine-k is a parameter of the prediction model that is populated by the set of data.

Claim 167: The non-transitory computer-readable medium of Claim 150, wherein only Tidal Volume (Set) is a parameter of the prediction model that is populated by the set of data.

Claim 168: The non-transitory computer-readable medium of Claim 150, wherein only Cholesterol (< 200) is a parameter of the prediction model that is populated by the set of data.

Claim 169: The non-transitory computer-readable medium of Claim 150, wherein only Fingerstick Glucose is a parameter of the prediction model that is populated by the set of data.

Claim 170: The non-transitory computer-readable medium of Claim 150, wherein only 0.9% Normal Saline 1000 ml is a parameter of the prediction model that is populated by the set of data.

Claim 171: The non-transitory computer-readable medium of Claim 150, wherein only Total Hourly Output is a parameter of the prediction model that is populated by the set of data.

Claim 172: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1528, chart 1531, chart 198, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 173: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 198, chart 20001, chart 682, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 174: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 20001, chart 20009, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 175: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 20009, chart 211, chart 682, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, and totalbal 26.

Claim 176: The system of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 211, chart 671, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 177: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 671, chart 682, chart 773, chart 779, chart 781, chart 785, chart 818, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 178: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 773, chart 779, chart 781, chart 785, chart 793, chart 811, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 179: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1529, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 793, chart 809, chart 818, chart 828, io 102, io 133, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 18, totalbal 19, totalbal 20, and totalbal 26.

Claim 180: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 809, chart 811, chart 818, chart 826, chart 828, io 102, io 133, io 55, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 20, and totalbal 26.

Claim 181: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 1162, chart 1531, chart 682, chart 779, chart 781, chart 785, chart 811, chart 818, chart 828, io 102, io 133, io 53, io 69, io 97, lab 50017, lab 50019, totalbal 1, totalbal 16, totalbal 19, totalbal 2, totalbal 20, and totalbal 26.

Claim 182: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 811, chart 818, chart 1532, lab 50030, and totalbal 26.

Claim 183: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50030, io 55, io 97, totalbal 2, and totalbal 16.

Claim 184: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 818, chart 1162, lab 50019, io 133, and totalbal 16.

Claim 185: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, chart 682, chart 1531, lab 50019, io 97, and totalbal 16.

Claim 186: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50019 and io 102.

Claim 187: The non-transitory computer-readable medium of Claim 150, wherein all of the parameters of the prediction model that are populated by the set of data are, as defined in MIMIC II database, lab 50017 and io 97.

Claim 188: The non-transitory computer-readable medium of Claim 150, wherein only lab 50019, as defined in MIMIC II database, is a parameter of the prediction model that is populated by the set of data.

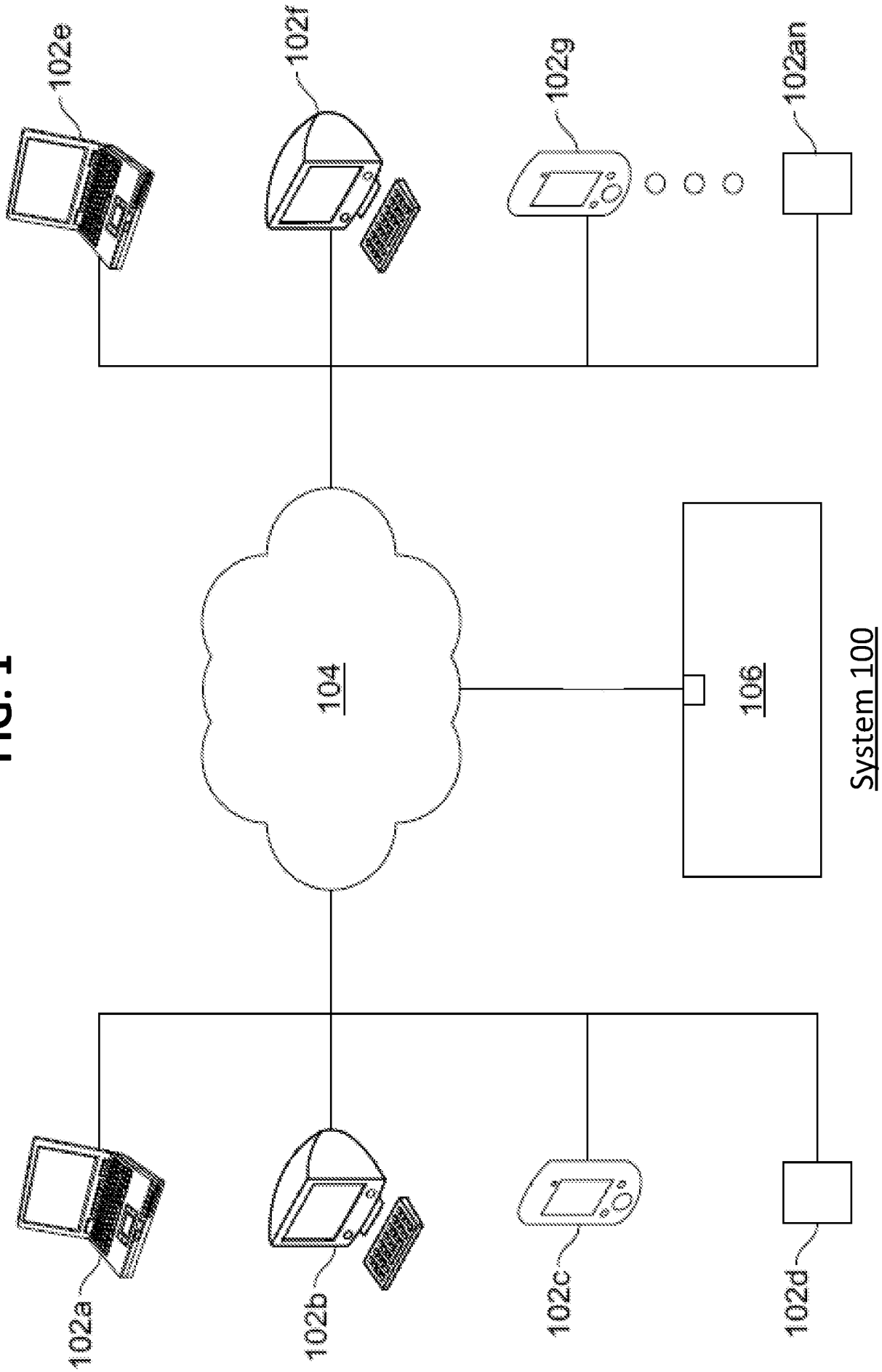
Claim 189: The non-transitory computer-readable medium of Claim 150, wherein only lab chart 682, as defined in MIMIC II database, is a parameter of the prediction model that is populated by the set of data.

Claim 190: The non-transitory computer-readable medium of Claim 150, wherein only a single parameter of the prediction model is populated by the data set.

Claim 191: The non-transitory computer-readable medium of Claim 150, wherein at least one of the parameters is a measurement related to a blood glucose level.

Claim 192: The non-transitory computer-readable medium of Claim 150, wherein at least one of the parameters is a measurement related to oxygen saturation in blood.

FIG. 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/023885

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/53; G01N 33/50; C12Q 1/68; G06F 19/00 (2017.01)
CPC - G01N 33/6893; G01N 2800/26; C12Q 2600/158; C12Q 1/6883; C12Q 2600/118 (2017.02)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/7.1; 435/6; 436/501; 702/19 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2015/121605 A1 (THE SECRETARY OF STATE FOR DEFENCE) 20 August 2015 (20.08.2015) entire document	1, 17, 33, 49-192 --- 2-16, 18-32, 34-48
Y	US 2015/0218640 A1 (IMMUNEXPRESS PTY LTD) 06 August 2015 (06.08.2015	2-16, 18-32, 34-48
A	US 2015/0269355 A1 (PEACH INTELLIHEALTH, INC.) 24 September 2015 (24.09.2015) entire document	1-192
A	US 9,091,698 B2 (BECTON, DICKINSON AND COMPANY) 28 July 2015 (28.07.2015) entire document	1-192
A	US 2012/0202240 A1 (DEIGNER et al) 09 August 2012 (09.08.2012) entire document	1-192
A	US 2011/0105350 A1 (GARRETT et al) 05 May 2011 (05.05.2011) entire document	1-192
A	US 2009/0203534 A1 (HOSSAIN et al) 13 August 2009 (13.08.2009) entire document	1-192
A	US 2008/0114576 A1 (JACKSON et al) 15 May 2008 (15.05.2008) entire document	1-192
A	US 2009/0149724 A1 (MARK et al) 11 June 2009 (11.06.2009) entire document	1-192
A	US 2011/0118569 A1 (SHI et al) 19 May 2011 (19.05.2011) entire document	1-192
A	US 2014/0046683 A1 (THERANOS, INC.) 13 February 2014 (13.02.2014) entire document	1-192

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 August 2017	28 AUG 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/023885

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet(s).

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/023885

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-48, drawn to a system for disease prediction.
Group II, claims 49-192, drawn to a system for disease prediction comprising populating parameters of the prediction model with values from the received set of data.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of the Group I invention: a dataset including data of a patient population, the data including for each of a plurality of patients of the patient population, values for a plurality of features and a diagnosis value of a diagnosis feature indicating whether a disease has been diagnosed; based on correlations between the values, select from the dataset a plurality of sub sets of the features as claimed therein is not present in the invention of Group II. The special technical feature of the Group II invention: output via the at least one interface a probability of the particular patient developing the disease within a particular time frame as claimed therein is not present in the invention of Group I.

Groups I and II lack unity of invention because even though the inventions of these groups require the technical feature of a system for disease prediction, the system comprising receive via the at least one interface a set of data associated with a particular patient; based on the received set of data, select one of a plurality of prediction models; execute the selected prediction model, this technical feature is not a special technical feature as it does not make a contribution over the prior art.

Specifically, US2015/0269355 A1 (TIDOR) 24 September 2015 (24.09.2015) teaches a system for disease prediction , the system comprising receive via the at least one interface a set of data associated with a particular patient; based on the received set of data, select one of a plurality of prediction models; execute the selected prediction model (Each patient receives a FitBit (Registered Trademark) activity and exercise monitor that uses Bluetooth (Registered Trademark) technology and the Internet to upload data to FitBit's servers; the patient also records their daily weight in the FitBit (Registered Trademark) application. Each patient is further instructed on how to report on their dietary intake using the MyFitnessPal (Registered Trademark) application. The system extracts daily data from the FitBit (Registered Trademark) and MyFitnessPal (Registered Trademark) databases for each patient and securely transfers the data to its own servers where it resides in encrypted form. The system's computational infrastructure parameterizes a diet-exercise-weight model for each patient. The model takes as input what the person has eaten (diet) and their level of activity (exercise), and predicts what their weight should be, assuming no fluid buildup. By comparing predicted to actual weight, the system flags patientswho are likely to be experiencing weight gain due to fluid buildup, and sends a notification to the health care system so individual follow up can be arranged, para. 0077).

Since none of the special technical features of the Group I or II inventions are found in more than one of the inventions, unity of invention is lacking.

专利名称(译)	临床参数在SIRS预测中的应用		
公开(公告)号	EP3433614A4	公开(公告)日	2019-12-11
申请号	EP2017771186	申请日	2017-03-23
[标]申请(专利权)人(译)	PEACH INTELLIHEALTH		
申请(专利权)人(译)	PEACH INTELLIHEALTH，INC.		
[标]发明人	HONG L S KLAUDYNE WOGAN GERALD VACCA LUIGI TIDOR BRUCE		
发明人	HONG, L.S, KLAUDYNE WOGAN, GERALD VACCA, LUIGI TIDOR, BRUCE		
IPC分类号	G01N33/53 G01N33/50 C12Q1/68 G06F19/00		
CPC分类号	G16H50/20 G16H50/70		
代理机构(译)	贝滕＆RESCH		
优先权	62/312339 2016-03-23 US		
其他公开文献	EP3433614A1		
外部链接	Espacenet		

摘要(译)

用于疾病预测的系统包括处理电路，该处理电路被配置为接收包括患者人群的数据的数据集，该数据包括该患者人群的多个患者中的每个患者，多个特征的值以及指示是否疾病的诊断值 已被诊断。 处理电路被配置为基于值之间的相关性，从数据集中选择特征的多个子集，并且对于至少一个子集的每一个，利用相应的子集和诊断执行机器学习过程。 值作为输入参数，执行生成相应的预测模型。 处理电路被配置为输出相应的预测模型。