

SEPSIS BIOMARKERS AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to diagnostic and/or prognostic biomarker or biomarkers for detection and/or prediction of sepsis.

BACKGROUND OF THE INVENTION

[0002] The following discussion of the background to the invention is intended to facilitate an understanding of the present invention. However, it should be appreciated that the discussion is not an acknowledgment or admission that any of the material referred to was published, known or part of the common general knowledge in any jurisdiction as at the priority date of the application.

[0003] Sepsis arises from a host response to an infection caused by bacteria or other infectious agents such as viruses, fungi and parasites. This response is called Systemic Inflammatory Response Syndrome (SIRS). Outcomes from sepsis are determined by the virulence of the invading pathogen and the host response, which may be over-exuberant resulting in collateral damage of organs and tissues. Typically, when sepsis arises, the body of the host is unable to break down clots that are formed in the lining of inflamed blood vessels, limiting blood flow to the organs, and subsequently leading to organ failure or gangrene.

[0004] Sepsis is a continuum of heterogeneous disease processes generally starting with infection, followed by SIRS, then sepsis, followed by severe sepsis and finally septic shock which causes multiple organ dysfunction and death. Worldwide incidence of sepsis continues to rise, with increasing concern in the elderly patients due to fast aging population. Approximately one-third to one-half of all severe sepsis patients succumb to their illness. Early stratification and timely intervention in patients with suspected infection before progression to

sepsis remains a critical clinical challenge to physicians worldwide as sepsis is often diagnosed at too late a stage.

[0005] Early diagnosis of sepsis is challenging because clinical signs of SIRS in sepsis are antedated by biochemical and immunological reactions. In addition, SIRS criteria are very generic in which border line outcomes result in diagnostic unclarity. Furthermore, infection is only one of the protean conditions that can lead to SIRS, the rest being sterile inflammation. Currently available standard laboratory signs of sepsis such as leukocytes, lactate, blood glucose and thrombocyte counts are non-specific. In about one-third of sepsis patients, the causative organism fails to be identified, further hampering early commencement of antimicrobial therapy or even worse, the liberal use of board-spectrum antibiotics which would perpetuate resistance to antimicrobial drugs.

[0006] Previous research to identify sepsis biomarkers such as cytokines, chemokines, acute phase proteins, soluble receptors and cell surface markers did not reliably differentiate between infectious from non-infectious causes of inflammation. It is a difficult to derive accurate biomarkers for diagnosis of sepsis because a host response of SIRS and to infection is regulated by multiple pathways, complicating efforts to derive accurate biomarkers. Furthermore, the number of useful prognostic biomarkers available is also very low.

[0007] Therefore, there is a need for robust, effective biomarkers or a biomarker for diagnosis and/or prognosis of sepsis, and states in the sepsis continuum, that overcome(s), or at least alleviate(s), the above-mentioned problems.

SUMMARY OF THE INVENTION

[0008] The present invention seeks to provide novel methods for detection and/or prognosis of sepsis, and states in the sepsis continuum, in a subject to ameliorate some of the difficulties with, and complement the current methods of detection and/or prediction of sepsis. The present invention further seeks to provide kits for detection and/or prognosis of sepsis, and states in the sepsis

continuum, in a subject.

[0009] The present invention also seeks to provide novel methods for assessing and/or predicting the severity of sepsis in a subject tested positive for sepsis. Preferably, the methods are for assessing whether a subject has, or is at risk of developing, one of a plurality of conditions selected from infection, mild sepsis and severe sepsis, and/or one of a plurality of conditions selected from the states in the sepsis continuum. The present invention further seeks to provide kits for assessing and/or predicting the severity of sepsis in a subject tested positive for sepsis.

[0010] The present invention is based on a multi-gene signature approach as a diagnostic biomarker derived from gene expression profiling in leukocytes isolated from patient blood samples, which provides a diagnostic that is significantly more accurate and proleptic than existent methods. The diagnostic biomarker comprising a set of genes collectively reflect broad-range and convergent effects of inflammatory responses, hormonal signaling, onset of endothelial dysfunction, blood coagulation, organ injury and the like.

[0011] The present invention relates to a set of genes which has been derived from a microarray genome wide expression profile, validated by qPCR assay. Surprisingly, hierarchical clustering of the microarray gene expression profiling results demonstrated significant differences in gene expression pattern of leukocytes among the different states in the sepsis continuum, namely, control, infection, non-infected Systemic Inflammatory Response Syndrome (SIRS) or also known as SIRS without infection, sepsis, severe sepsis, cryptic shock and septic shock patients. Differentially expressed genes during sepsis were derived from microarray gene profiling, and a panel of genes were shortlisted from the initial 33,000. Furthermore and surprisingly, analytical validation using qPCR indicates that this panel of genes or biomarkers is progressively dysregulated, such as up- or down-regulation, in subjects across the sepsis continuum, which correlates to microarray results. Gene expression changes in leukocytes can be clearly observed and utilized for diagnosis and/or prognosis of sepsis and states in the sepsis continuum.

[0012] In addition to the above, surprisingly, any number of the predetermined panel of genes or biomarkers can be used, and in any combination, for the diagnosis and/or prognosis of sepsis and the states in the sepsis continuum.

[0013] In accordance with a first aspect of the invention, there is provided a method of detecting or predicting sepsis in a subject, the method comprising:

- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
- ii. comparing the level measured to a reference level of a corresponding biomarker,

wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof,

wherein a difference between the level measured in the first sample and the reference level is indicative of sepsis being present in the first sample.

[0014] Preferably, the presence of sepsis is determined by detecting in the subject an increase in the level of the at least one biomarker measured in the first

sample, the at least one biomarker selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof, as compared to the reference level of the corresponding biomarker.

[0015] Preferably, the presence of sepsis is determined by detecting in the subject a decrease in the level of the at least one biomarker measured in the first sample, the at least one biomarker selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof, as compared to the reference level of the corresponding biomarker.

[0016] Preferably, the reference level is the level of the corresponding biomarker in a second sample isolated from at least one subject with no sepsis.

[0017] Preferably, the comparing step comprises applying a decision rule to determine or predict the presence or absence of sepsis in the subject.

[0018] In accordance with a second aspect of the invention, there is

provided a method of detecting or predicting whether a subject has one of a plurality of conditions selected from a group consisting of: control, infection, non-infected systemic inflammatory response syndrome (SIRS), mild sepsis, severe sepsis, septic shock and cryptic shock, the method comprising:

- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
- ii. comparing the level measured to a reference level of a corresponding biomarker,

wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof,

wherein the level measured in the first sample is statistically substantially similar to the reference level is indicative of whether the subject has one of the conditions.

[0019] Preferably, the reference level is the level of a corresponding biomarker in a second sample isolated from at least one subject selected from a group consisting of: a control subject, an infection positive subject, a non-infected SIRS positive subject, a mild sepsis positive subject, a severe sepsis positive subject and a cryptic shock positive subject.

[0020] Preferably, the comparing step comprises applying a decision rule to determine or predict whether the subject has one of the conditions.

[0021] In accordance with a third aspect of the invention, there is provided a kit for performing the method of the first aspect, the kit comprising:

- i. at least one reagent capable of specifically binding to the at least one biomarker to quantify the level of the biomarker in the first sample of a subject; and
- ii. a reference standard indicating the reference level of the corresponding biomarker.

[0022] Preferably, the at least one reagent comprises at least one antibody capable of specifically binding to the at least one biomarker.

[0023] Preferably, the kit further comprises at least one additional reagent capable of specifically binding at least one additional biomarker in the first sample, and a reference standard indicating a reference level of a corresponding at least one additional biomarker.

[0024] In accordance with a fourth aspect of the invention, there is provided a kit for performing the method of the second aspect, the kit comprising:

- i. at least one reagent capable of specifically binding to the at least one biomarker to quantify the level of the biomarker in the first sample of a subject; and
- ii. a reference standard indicating the reference level of the corresponding biomarker.

[0025] Preferably, the at least one reagent comprises at least one antibody capable of specifically binding to the at least one biomarker.

[0026] Preferably, the kit further comprises at least one additional reagent capable of specifically binding at least one additional biomarker in the first sample, and a reference standard indicating a reference level of a corresponding at least one additional biomarker.

[0027] In accordance with a fifth aspect of the invention, there is provided a kit for detecting or predicting sepsis in a subject, comprising an antibody capable of binding selectively to at least one biomarker in a first sample isolated from the subject and reagents for detection of a complex formed between the antibody and complement component of the at least one biomarker, wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof, and a reference standard indicating a reference level of a corresponding biomarker, wherein a difference between a level of the at least one biomarker measured in the first sample and the reference level is indicative of sepsis being present in the first sample.

[0028] Preferably, the reference level is the level of the corresponding biomarker in a second sample isolated from at least one subject with no sepsis.

[0029] In accordance with a sixth aspect of the invention, there is provided a kit for detecting or predicting whether a subject has one of a plurality of conditions selected from a group consisting of: control, infection, non-infected systemic inflammatory response syndrome (SIRS), mild sepsis, severe sepsis, septic shock and cryptic shock, comprising an antibody comprising capable of binding selectively to at least one biomarker in a first sample isolated from the

subject and reagents for detection of a complex formed between the antibody and complement component of the at least one biomarker, wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof, and a reference standard indicating a reference level of a corresponding biomarker, wherein a level of the at least one biomarker measured in the first sample is statistically substantially similar to the reference level is indicative of whether the subject has one of the conditions.

[0030] Preferably, the reference level is the level of a corresponding biomarker in a second sample isolated from at least one subject selected from a group consisting of: a control subject, an infection positive subject, a non-infected SIRS positive subject, a mild sepsis positive subject, a severe sepsis positive subject and a cryptic shock positive subject.

[0031] In accordance with a seventh aspect of the invention, there is provided a method of detecting or predicting sepsis in a subject, the method comprising:

- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and

- ii. comparing the level measured to a reference level of a corresponding biomarker,

wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one or more of the sequences of (a), (b), or a complement thereof,

wherein a difference between the level measured in the first sample and the reference level is indicative of sepsis being present in the first sample.

[0032] In accordance with an eighth aspect of the invention, there is provided a method of detecting or predicting whether a subject has one of a plurality of conditions selected from a group consisting of: control, infection, non-infected systemic inflammatory response syndrome (SIRS), mild sepsis, severe sepsis, septic shock and cryptic shock, the method comprising:

- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
- ii. comparing the level measured to a reference level of a corresponding biomarker,

wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one or more of the sequences of (a), (b), or a complement thereof,

wherein the level measured in the first sample is statistically substantially similar to the reference level is indicative of whether the subject has one of the conditions.

[0033] In accordance with another aspect of the present invention, there is provided at least one gene selected from a predetermined panel of genes for diagnosis of sepsis in a subject.

[0034] Another aspect of the present invention provides at least one gene selected from a predetermined panel of genes for prognosis of sepsis in a subject.

[0035] Another aspect of the present invention provides a method for detecting, or predicting, sepsis in a subject. The method generally comprises measuring the level of at least one sepsis continuum marker expression product of at least one gene selected from a predetermined panel of genes in a suitable fluid sample obtained from the subject and comparing the level measured to the level of a corresponding sepsis continuum marker expression product in at least one

control subject, the control subject being a normal subject, wherein a difference between the level of the at least one sepsis continuum marker expression product and the level of the corresponding sepsis continuum marker expression product is indicative of sepsis being present in the subject.

[0036] Another aspect of the present invention provides a method for assessing whether a subject has one of a plurality of conditions selected from infection, mild sepsis and severe sepsis. The method generally comprise the steps of measuring the level of at least one sepsis continuum marker expression product of at least one gene selected from a predetermined panel of genes in a suitable fluid sample obtained from the subject and comparing the level measured to the level of a corresponding sepsis continuum marker expression product in a plurality of control subjects, the control subjects being at least one infection positive subject, at least one mild sepsis positive subject and at least one severe sepsis positive subject, wherein when the level of the at least one expression product is statistically substantially similar to the level of the corresponding sepsis continuum marker expression product of any one of the control subjects, it is indicative of whether the subject has one of the conditions.

[0037] Another aspect of the invention provides a kit for detection and/or prognosis of sepsis in a subject, comprising an antibody capable of binding selectively to at least one sepsis continuum marker expression product of at least one gene selected from a predetermined panel of genes in a suitable fluid sample obtained from the subject and reagents for detection of a complex formed between the antibody and a complement component of the at least one expression product.

[0038] Another aspect of the invention provides a kit for assessing and/or predicting the severity of sepsis in a subject, comprising an antibody capable of binding selectively to at least one sepsis continuum marker expression product of at least one gene selected from a predetermined panel of genes in a suitable fluid sample obtained from the subject and reagents for detection of a complex formed between the antibody and a complement component of the at least one expression product.

[0039] Preferably, the kit is for assessing whether a subject has, or is at

risk of developing, one of a plurality of conditions selected from infection, mild sepsis and severe sepsis.

[0040] Advantageously, the at least one gene is selected from a predetermined panel of genes comprising of: Homo sapiens acyl-CoA synthetase long-chain family member 1 (ACSL1) gene, Homo sapiens annexin A3 (ANXA3) gene, Homo sapiens cysteine-rich transmembrane module containing 1 (CYSTM1) gene, Homo sapiens chromosome 19 open reading frame 59 (C19orf59) gene, Homo sapiens colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage) (CSF2RB) gene, Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like (DDX60L) gene, Homo sapiens Fc fragment of IgG, high affinity Ib, receptor (CD64) (FCGR1B) gene, Homo sapiens free fatty acid receptor 2 (FFAR2) gene, Homo sapiens formyl peptide receptor 2 (FPR2) gene, Homo sapiens heat shock 70kDa protein 1B (HSPA1B) gene, Homo sapiens interferon induced transmembrane protein 1 (IFITM1) gene, Homo sapiens interferon induced transmembrane protein 3 (IFITM3) gene, Homo sapiens interleukin 1, beta (IL1B) gene, Homo sapiens interleukin 1 receptor antagonist (IL1RN) gene, Homo sapiens leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 5 (LILRA5) gene, Homo sapiens leucine-rich alpha-2-glycoprotein 1 (LRG1) gene, Homo sapiens myeloid cell leukemia sequence 1 (BCL2-related) (MCL1) gene, Homo sapiens NLR family, apoptosis inhibitory protein (NAIP) gene, Homo sapiens nuclear factor, interleukin 3 regulated (NFIL3) gene, Homo sapiens 5'-nucleotidase, cytosolic III (NT5C3) gene, Homo sapiens 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) gene, Homo sapiens phospholipid scramblase 1 (PLSCR1) gene, Homo sapiens prokineticin 2 (PROK2) gene, Homo sapiens RAB24, member RAS oncogene family (RAB24) gene, Homo sapiens S100 calcium binding protein A12 (S100A12) gene, Homo sapiens selectin L (SELL) gene, Homo sapiens solute carrier family 22 (organic cation/ergothioneine transporter), member 4 (SLC22A4) gene, Homo sapiens superoxide dismutase 2, mitochondrial (SOD2) gene, Homo sapiens SP100 nuclear antigen (SP100) gene, Homo sapiens toll-like receptor 4 (TLR4) gene, Homo sapiens chemokine (C-C motif) ligand 5 (CCL5) gene, Homo sapiens chemokine (C-C motif) receptor 7 (CCR7) gene, Homo sapiens CD3d molecule, delta (CD3-TCR complex) (CD3D) gene, Homo sapiens CD6 molecule

(CD6) gene, Homo sapiens Fas apoptotic inhibitory molecule 3 (FAIM3) gene, Homo sapiens Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide (FCER1A) gene, Homo sapiens granzyme K (granzyme 3; tryptase II) (GZMK) gene, Homo sapiens interleukin 7 receptor (IL7R) gene, Homo sapiens killer cell lectin-like receptor subfamily B, member 1 (KLRB1) gene, Homo sapiens mal, T-cell differentiation protein (MAL) gene.

[0041] Advantageously, the at least one gene selected from the predetermined panel of genes is either up-regulated or down-regulated in a subject with sepsis.

[0042] Advantageously, the at least one gene selected from the predetermined panel of genes is progressively up-regulated or down-regulated from control and SIRS without infection, to infection without SIRS, to mild sepsis to severe sepsis.

[0043] Advantageously, any number of the predetermined panel of genes can be selected or used, and in any combination, for the diagnosis and/or prognosis of sepsis.

[0044] Advantageously, any number of the predetermined panel of genes can be selected or used, and in any combination, for assessing and/or predicting the severity of sepsis in a subject tested positive for sepsis.

[0045] Preferably, the at least one sepsis continuum marker transcript is selected from the group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences listed in **List 1**; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences listed in **List 1** that encodes a polypeptide comprising its corresponding amino acid sequence.

[0046] Advantageously, the present invention can be used to distinguish between patients with no sepsis and patients with sepsis. The present invention can also be used to distinguish patients with sepsis and patients with severe sepsis.

[0047] Advantageously, the present invention can be used for the early detection and diagnosis of sepsis, and also the monitoring of patients for an improvement of treatment and outcome for such patients.

[0048] Advantageously, the present invention can be used to identify and/or classify a subject or patient as a candidate for sepsis therapy.

[0049] Other aspects and features of the present invention will become apparent to those of ordinary skill in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] In the figures, which illustrate, by way of example only, embodiments of the present invention, are as follows.

[0051] **FIGURE 1:** Relative average fold change of infection (without SIRS), mild and severe sepsis samples over control by qPCR. (A) 30 up-regulated genes; and (B) 10 down-regulated genes.

[0052] **FIGURE 2:** Overlapping genes identified from four different gene classification methods.

[0053] **FIGURE 3:** Unsupervised hierarchical clustering heatmap of genes with up- or down- regulated expression level in sepsis continuum.

[0054] **FIGURE 4:** Boxplots based on 6 Models (A-F) which allow the stratification of septic/non septic patients. A predetermined cut off between Sepsis/non-sepsis, indicated by the respective horizontal lines, is based on a decision rule for highest total accuracy achievable. For each model a training set based on 100 samples was created (left) and a blinded test of 61 samples was used (right) to validate the models. The Models are:

- (A) using 40 genes and HPRT1 as normalization housekeeping gene.

- (B) using 8 genes and HPRT1 as normalization housekeeping gene.
- (C) using 40 genes and GAPDH as normalization housekeeping gene.
- (D) using 8 genes and GAPDH as normalization housekeeping gene.
- (E) using 40 genes and both HPRT1 and GAPDH as normalization housekeeping genes.
- (F) using 11 genes and both HPRT1 and GAPDH as normalization housekeeping genes.

[0055] **FIGURE 5:** Boxplot representing 85 sepsis patients based on either 37 genes (A) or 14 genes (B). Weight scoring system was implemented using 2 models which allow the segregation of severe sepsis from mild sepsis.

[0056] **FIGURE 6:** Average plasma protein concentration (S100A12) in patients selected from the group consisting of control, infection, mild sepsis and severe sepsis/septic shock, indicating a correlation between severity of Sepsis and protein concentration.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0057] The present invention uses a multi-gene signature approach as a diagnostic biomarker derived from gene expression profiling in leukocytes isolated from blood samples of subjects which provides a diagnostic that is significantly more accurate and faster than existing methods. Advantageously, gene expression profiling overcomes, or at least alleviates, the problem of delayed diagnosis of sepsis as the up- or down-regulation of genes occur before the synthesis of functional gene products such as pro-inflammatory proteins. Advantageously, the present invention can reliably and accurately categorise an individual with sepsis or provide prognostic clues on the progression of the syndrome, thereby allowing for more effective therapeutic intervention.

[0058] A cohort study was carried out. The objectives of the cohort study

relating to the study of emergency department patients with sepsis include (i) deriving and validating a gene expression panel that are differentially expressed in the leukocytes of patients with and without sepsis to enhance early diagnosis of sepsis; and (ii) investigating the prognostic value of the gene expression panel to guide treatment in sepsis by predicting the severity of sepsis at its onset.

[0059] Advantageously, there is provided a method of detecting or predicting sepsis in a subject, the method comprises

- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
- ii. comparing the level measured to a reference level of a corresponding biomarker,

wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof,

wherein a difference between the level measured in the first sample and the reference level is indicative of sepsis being present in the first sample.

[0060] Advantageously, there is also provided a method of detecting or

predicting whether a subject has one of a plurality of conditions selected from a group consisting of: control, infection, non-infected systemic inflammatory response syndrome (SIRS), mild sepsis, severe sepsis, septic shock and cryptic shock, the method comprises

- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
- ii. comparing the level measured to a reference level of a corresponding biomarker,

wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment, homologue, variant or derivative thereof; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), (b), or a complement thereof,

wherein the level measured in the first sample is statistically substantially similar to the reference level is indicative of whether the subject has one of the conditions.

[0061] As used herein, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise.

[0062] The use of “or”, “/” means “and/or” unless stated otherwise. Furthermore, the use of the terms “including” and “having” as well as other forms

of those terms, such as “includes”, “included”, “has”, and “have” are not limiting.

[0063] “Sample”, “test sample”, “specimen”, “sample used from a subject”, and “patient sample”, including the plural referents, as used herein may be used interchangeably and may be a sample of blood, tissue, urine, serum, plasma, amniotic fluid, cerebrospinal fluid, placental cells or tissue, endothelial cells, leukocytes, or monocytes. The sample can be used directly as obtained from a patient or subject can be pre-treated, such as by filtration, distillation, extraction, concentration, centrifugation, inactivation of interfering components, addition of reagents, and the like, to modify the character of the sample in some manner as discussed herein or otherwise as is known in the art.

[0064] Any cell type, tissue, or bodily fluid may be utilised to obtain a sample. Such cell types, tissues, and fluid may include sections of tissues such as biopsy and autopsy samples, frozen sections taken for histological purposes, blood (such as whole blood), plasma, serum, sputum, stool, tears, mucus, saliva, bronchoalveolar lavage (BAL) fluid, hair, skin, red blood cells, platelets, interstitial fluid, ocular lens fluid, cerebral spinal fluid, sweat, nasal fluid, synovial fluid, menses, amniotic fluid, semen, etc. Cell types and tissues may also include lymph fluid, ascetic fluid, gynaecological fluid, urine, peritoneal fluid, cerebrospinal fluid, a fluid collected by vaginal rinsing, or a fluid collected by vaginal flushing. A tissue or cell type may be provided by removing a sample of cells from an animal, but can also be accomplished by using previously isolated cells (for example, isolated by another person, at another time, and/or for another purpose). Archival tissues, such as those having treatment or outcome history, may also be used. Protein or nucleotide isolation and/or purification may or may not be necessary.

[0065] A nucleic acid or fragment thereof is “substantially homologous” (“or substantially similar”) to another if, when optimally aligned (with appropriate nucleotide insertions or deletions) with the other nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95-98% of the nucleotide bases.

[0066] Alternatively, substantial homology or (identity) exists when a nucleic acid or fragment thereof will hybridise to another nucleic acid (or a complementary strand thereof) under selective hybridisation conditions, to a strand, or to its complement. Selectivity of hybridisation exists when hybridisation that is substantially more selective than total lack of specificity occurs. Typically, selective hybridisation will occur when there is at least about 55% identity over a stretch of at least about 14 nucleotides, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will often be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides.

[0067] Thus, polynucleotides of the invention preferably have at least 75%, more preferably at least 85%, more preferably at least 90% homology to the sequences shown in List 1 or the sequence listings herein. More preferably there is at least 95%, more preferably at least 98%, homology. Nucleotide homology comparisons may be conducted as described below for polypeptides. A preferred sequence comparison program is the GCG Wisconsin Best fit program described below. The default scoring matrix has a match value of 10 for each identical nucleotide and -9 for each mismatch. The default gap creation penalty is -50 and the default gap extension penalty is -3 for each nucleotide.

[0068] In the context of the present invention, a homologue or homologous sequence is taken to include a nucleotide sequence which is at least 60, 70, 80 or 90% identical, preferably at least 95 or 98% identical at the amino acid level over at least 20, 50, 100, 200, 300, 500 or 1000 nucleotides with the nucleotides sequences set out in the sequence listings or in List 1 below. In particular, homology should typically be considered with respect to those regions of the sequence that encode contiguous amino acid sequences known to be essential for the function of the protein rather than non-essential neighbouring sequences. Preferred polypeptides of the invention comprise a contiguous sequence having greater than 50, 60 or 70% homology, more preferably greater than 80, 90, 95 or

97% homology, to one or more of the nucleotides sequences set out in the sequences. Preferred polynucleotides may alternatively or in addition comprise a contiguous sequence having greater than 80, 90, 95 or 97% homology to the sequences set out in the sequence listings or in List 1 below that encode polypeptides comprising the corresponding amino acid sequences.

[0069] Other preferred polynucleotides comprise a contiguous sequence having greater than 40, 50, 60, or 70% homology, more preferably greater than 80, 90, 95 or 97% homology to the sequences set out that encode polypeptides comprising the corresponding amino acid sequences.

[0070] Nucleotide sequences are preferably at least 15 nucleotides in length, more preferably at least 20, 30, 40, 50, 100 or 200 nucleotides in length.

[0071] Generally, the shorter the length of the polynucleotide, the greater the homology required to obtain selective hybridization. Consequently, where a polynucleotide of the invention consists of less than about 30 nucleotides, it is preferred that the % identity is greater than 75%, preferably greater than 90% or 95% compared with the nucleotide sequences set out in the sequence listings herein or in List 1 below. Conversely, where a polynucleotide of the invention consists of, for example, greater than 50 or 100 nucleotides, the % identity compared with the sequences set out in the sequence listings herein or List 1 below may be lower, for example greater than 50%, preferably greater than 60 or 75%.

[0072] The "polynucleotide" compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.), charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g., polypeptides), intercalators (e.g., acridine, psoralen, etc.), chelators,

alkylators, and modified linkages (e.g., alpha anomeric nucleic acids, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

[0073] The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not refer to, or exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations, and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, natural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring.

[0074] In the context of the present invention, a homologous sequence is taken to include an amino acid sequence which is at least 60, 70, 80 or 90% identical, preferably at least 95 or 98% identical at the amino acid level over at least 20, 50, 100, 200, 300 or 400 amino acids with the sequences set out in the sequence listings or in List 1 below that encode polypeptides comprising the corresponding amino acid sequences. In particular, homology should typically be considered with respect to those regions of the sequence known to be essential for the function of the protein rather than non-essential neighbouring sequences. Preferred polypeptides of the invention comprise a contiguous sequence having greater than 50, 60 or 70% homology, more preferably greater than 80 or 90% homology, to one or more of the corresponding amino acids.

[0075] Other preferred polypeptides comprise a contiguous sequence having greater than 40, 50, 60, or 70% homology, of the sequences set out in the sequence listings or in List 1 below that encode polypeptides comprising the corresponding amino acid sequences. Although homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions), in the context of the present invention it is preferred to express homology in terms of sequence identity. The terms "substantial

homology" or "substantial identity", when referring to polypeptides, indicate that the polypeptide or protein in question exhibits at least about 70% identity with an entire naturally-occurring protein or a portion thereof, usually at least about 80% identity, and preferably at least about 90 or 95% identity.

[0076] Homology comparisons can be conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These commercially available computer programs can calculate % homology between two or more sequences.

[0077] Percentage (%) homology may be calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in one sequence directly compared with the corresponding amino acid in the other sequence, one residue at a time. This is called an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of residues (for example less than 50 contiguous amino acids).

[0078] Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause the following amino acid residues to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence comparison methods are designed to produce optimal alignments that take into consideration possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting "gaps" in the sequence alignment to try to maximise local homology.

[0079] However, these more complex methods assign "gap penalties" to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared sequences - will achieve a higher score than one with many gaps. "Affine gap costs" are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimised alignments with

fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is preferred to use the default values when using such software for sequence comparisons. For example when using the GCG Wisconsin Best fit package (see below) the default gap penalty for amino acid sequences is -12 for a gap and -4 for each extension.

[0080] Calculation of maximum % homology therefore firstly requires the production of an optimal alignment, taking into consideration gap penalties. A suitable computer program for carrying out such an alignment is the GCG Wisconsin Best fit package (University of Wisconsin, U.S.A.; Devereux *et al.*, 1984, Nucleic Acids Research 12:387). Examples of other software that can perform sequence comparisons include, but are not limited to, the BLAST package (see Ausubel *et al.*, 1999 *ibid* – Chapter 18), FASTA (Atschul *et al.*, 1990, J. Mol. Biol., 403-410) and the GENWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (see Ausubel *et al.*, 1999 *ibid*, pages 7-58 to 7-60). However it is preferred to use the GCG Bestfit program.

[0081] Although the final % homology can be measured in terms of identity, the alignment process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled similarity score matrix is generally used that assigns scores to each pair-wise comparison based on chemical similarity or evolutionary distance. An example of such a matrix commonly used is the BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin programs generally use either the public default values or a custom symbol comparison table if supplied (see user manual for further details). It is preferred to use the public default values for the GCG package, or in the case of other software, the default matrix, such as BLOSUM62.

[0082] Once the software has produced an optimal alignment, it is possible to calculate % homology, preferably % sequence identity. The software typically does this as part of the sequence comparison and generates a numerical result.

[0083] A polypeptide "fragment," "portion" or "segment" is a stretch of amino acid residues of at least about five to seven contiguous amino acids, often at least about seven to nine contiguous amino acids, typically at least about nine

to 13 contiguous amino acids and, most preferably, at least about 20 to 30 or more contiguous amino acids.

[0084] Preferred polypeptides of the invention have substantially similar function to the sequences set out in the sequence listings or in List 1 below. Preferred polynucleotides of the invention encode polypeptides having substantially similar function to the sequences set out in the sequence listings or in List 1 below. "Substantially similar function" refers to the function of a nucleic acid or polypeptide homologue, variant, derivative or fragment of the sequences set out in the sequence listings or in List 1 below, with reference to the sequences set out in the sequence listings or in List 1 below or the sequences set out in the sequence listings or in List 1 below that encode polypeptides comprising corresponding amino acid sequences.

[0085] Nucleic acid hybridisation will be affected by such conditions as salt concentration, temperature, or organic solvents, in addition to the base composition, length of the complementary strands, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. Stringent temperature conditions will generally include temperatures in excess of 30 degrees Celsius, typically in excess of 37 degrees Celsius, and preferably in excess of 45 degrees Celsius. Stringent salt conditions will ordinarily be less than 1000 mM, typically less than 500 mM, and preferably less than 200 mM. However, the combination of parameters is much more important than the measure of any single parameter. An example of stringent hybridization conditions is 65°C and 0.1xSSC (1xSSC = 0.15 M NaCl, 0.015 M sodium citrate pH 7.0).

[0086] "Subject", "patient", and "individual" including the plural referents, as used herein may be used interchangeably and refers to any vertebrate, including but not limited to a mammal. In some embodiments, the subject may be a human or a non-human. The subject or patient may or may not be undergoing other forms of treatment.

[0087] "Control" or "controls" as used herein refers to any condition unrelated to any infective cause; no underlying chronic inflammatory condition,

autoimmune disease or immunological disorder, for example, asthma, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus (SLE), type 1 diabetes mellitus, and the like.

[0088] “Systemic Inflammatory Response Syndrome (hereinafter referred to as “SIRS”) without infection” or “non-infected SIRS” as used herein fulfils at least two of the four SIRS criteria (see Table 2 below), and there is no clinical/radiological evidence of infection.

[0089] “Infection without SIRS” and “infection” as used herein, may be used interchangeably, does not fulfil at least two of the four SIRS criteria in Table 2 below. There is also clinical/radiological suspicion or confirmation of infection. Patients with such a condition may present symptoms and signs of upper respiratory tract infection/chest infection/pneumonia (including productive cough, runny nose, sore throat, infiltrates on the chest X-ray), urinary tract infection (including cloudy urine, dysuria, positive nitrites in the urinalysis), gastroenteritis (including diarrhoea, vomiting, abdominal cramps), cellulitis/abscess (including redness, swelling, pain, erythema of skin).

[0090] “Mild sepsis” as used herein fulfils at least two of the four SIRS criteria in Table 2 below, and there is clinical/radiological suspicion or confirmation of infection. The term also refers to SIRS with infection.

[0091] “Severe sepsis” as used herein refers to sepsis with serum lactate > 2 mmol/L or evidence of > 1 organ dysfunction (see Table 3 below).

[0092] “Cryptic shock” as used herein refers to sepsis with serum lactate > 4 mmol/L without hypotension.

[0093] “Septic shock” as used herein refers to sepsis with hypotension despite 1 litre infusion of intravenous crystalloid.

[0094] “States” or “conditions” of the sepsis continuum as used herein refers to control, infection (without SIRS), SIRS without infection, mild sepsis, severe sepsis, cryptic shock and septic shock. “Sepsis” as used herein refers to one or more of the states or conditions comprising mild sepsis, severe sepsis,

cryptic shock and septic shock. For example, if a subject is said to have sepsis, or predicted to have sepsis, the subject may be suffering from mild sepsis, or severe sepsis, or cryptic shock or septic shock. "Non-sepsis" or "no sepsis" as used herein refers to one or more of the states or conditions comprising control, infection and SIRS without infection. For example, if a subject is said to have no sepsis, the subject may be a control or has an infection or has SIRS without infection.

[0095] "Predetermined cut off" or "cut off" including the plural referents, as used herein refers to an assay cut off value that is used to assess diagnostic, prognostic, or therapeutic efficacy results by comparing the assay results against the predetermined cut off/cut off, where the predetermined cut off/cut off already has been linked or associated with various clinical parameters (for example, presence of disease/condition, stage of disease/condition, severity of disease/condition, progression, non-progression, or improvement of disease/condition, etc.). The disclosure provides exemplary predetermined cut offs/cut offs. However, it would be appreciated that cut off values may vary depending on the nature of the assay (for example, antibodies employed, reaction conditions, sample purity, etc.). Furthermore, it would be appreciated that the disclosure herein may be adapted for other assays, such as immunoassays to obtain immunoassay-specific cut off values for those other assays based on the description provided by this disclosure. Whereas the precise value of the predetermined cut off/cut off may vary between assays, the correlations as described herein should be generally applicable.

[0096] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. For example, any nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics, biotechnology, statistics and protein and nucleic acid chemistry and hybridisation described herein are those that are well known and commonly used in the art. The meaning and scope of the terms should be clear; in the event however of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic

definition. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

1. Materials and Methods

1.1. Patient cohort

[0097] A cohort study of patients along with the entire sepsis continuum in the National University Hospital of Singapore (“NUH”), Emergency Department (“ED”) was carried out. Admitted patients were followed-up in the inpatient units. Healthy controls and those with SIRS but without evidence of infection were also recruited to demonstrate differentiation of biomarkers for early diagnosis.

[0098] Subjects identified to fulfill the inclusion criteria for recruitment were approached to participate in this study. After informed consent was obtained from subjects, 12mL of blood was extracted into EDTA tubes and transported on ice to Acumen Research Laboratories (“ARL”). Samples were processed for RNA isolation within 30 minutes after blood collection. Patients who were discharged directly from the ED were tracked for any clinical recurrence of their disease within 30 days to ensure the diagnostic accuracy of the sample of biomarkers that are extracted. All patients that enrolled into the study were followed up after 30 days for final review, to ensure the diagnostic accuracy at recruitment.

[0099] Table 1 below shows the inclusion criteria for recruitment of subjects for the cohort study.

Table 1: Inclusion criteria (adults 21 years and above) for patients into categories in sepsis continuum.

Patient Category	Criteria
Controls	• Matched for age and gender • Presents to the ED with condition unrelated to any infective cause; no underlying chronic inflammatory condition, autoimmune disease or immunological disorder (e.g. asthma, rheumatoid arthritis, inflammatory bowel disease, SLE, type I diabetes mellitus)
SIRS without infection	• Fulfils at least 2 of the 4 SIRS criteria (see Table 2) • No clinical/radiological evidence of infection

Infection without SIRS	- Does not fulfill at least 2 of the 4 SIRS criteria - Clinical/radiological suspicion or confirmation of infection - Patients may present with symptoms and signs of upper respiratory tract infection/chest infection/pneumonia (productive cough, runny nose, sore throat, infiltrates on the chest X-ray), urinary tract infection (cloudy urine, dysuria, positive nitrites in the urinalysis), gastroenteritis (diarrhoea, vomiting, abdominal cramps), cellulitis/abscess (redness, swelling, pain, erythema of skin)
Mild Sepsis	- Fulfill at least 2 of the 4 SIRS criteria - Clinical/radiological suspicion or confirmation of infection
Severe sepsis	Sepsis with serum lactate > 2 mmol/L OR evidence of > 1 organ dysfunction (see Table 3)
Cryptic shock	Sepsis with serum lactate > 4 mmol/L without hypotension
Septic shock	Sepsis with hypotension despite 1 litre infusion of intravenous crystalloid

[00100] The exclusion criteria for recruitment of subjects for the cohort study includes the following: Age below 21 years, known pregnancy, prisoners, do-not-attempt resuscitation status, requirement for immediate surgery, active chemotherapy, haematological malignancy, treating physician deems aggressive care unsuitable, those unable to give informed consent or unable to comply with study requirements.

[00101] The four criteria for SIRS are shown in Table 2 below.

Table 2: The four criteria for SIRS

Systemic Inflammatory Response Syndrome (SIRS):	
1.	A temperature > 38°C or < 36°C
2.	Respirations > 20 breaths/min or partial pressure of CO ₂ of < 32 mmHg on the arterial blood gas
3.	A pulse rate > 90 beats/min
4.	A white blood cell count > 12,000 cells/mm ³ or < 4,000 cells/mm ³

[00102] The indicators of organ dysfunction are shown in Table 3 below.

Table 3: Indicators of organ dysfunction

Organ dysfunction:	
1.	PaO ₂ /FiO ₂ < 300
2.	Creatinine > 176 µmol/L or increase of more than 44 µmol/L from baseline
3.	Platelet <100 x 10 ⁹ /L
4.	INR > 1.5
5.	PTT > 60 seconds
6.	Total bilirubin > 34 µmol/L

1.2. Collection of blood samples from patients

[00103] A total of 12 mL of whole blood was drawn from each patient into four EDTA-coated blood collection tubes. Whole blood was transported on ice and RNA isolation was carried out within 30 minutes of sample collection.

1.3. RNA sample preparation

1.3.1. RNA extraction from leukocytes

[00104] Leukocyte RNA purification Kit (Norgen Biotek Corporation) was used according to the manufacturer's instruction for leukocytes RNA extraction.

1.3.2. RNA quality control and storage

[00105] RNA concentration and quality were determined using Nanodrop 2000 (Thermo Fisher Scientific). The RNA concentration, 260/280 and 260/230 ratios were recorded. The RNA was then stored in RNase and DNase free cryotube in liquid nitrogen.

[00106] A bioanalyzer (Agilent) was used in addition to Nanodrop to check the RNA quality of samples that was used in microarray studies. The RNA Integrity Number (RIN) of each RNA sample was obtained and images produced by the bioanalyzer after each electrophoretic run was analysed.

1.4. Pre-processing and analysis of gene expression microarray

[00107] Whole-genome gene expression microarray was performed on Illumina® Human HT-12 v4 BeadChip. Each array covers more than 47,000 transcripts and known splice variants across the human transcriptome (NCBI RefSeq Release 38).

[00108] In brief, 500 ng of total RNA purified from patient blood samples were amplified and labeled using the Illumina TotalPrep RNA Amplification kit (Ambion) according to the manufacturer's instructions. A total of 750 ng of labelled cRNA was then prepared for hybridization to the Illumina Human HT-12 v4 Expression BeadChip. After hybridization, BeadChips were scanned on a BeadArray Reader using BeadScan software v3.2, and the data was uploaded into GenomeStudio Gene Expression Module software v1.6 for further analysis.

[00109] Pre-processing and subsequent bioinformatics analyses were performed using R software and lumi package was to adjust background signals, quantile-normalization, and variance-stabilizing transformation of the raw gene expression data.

[00110] Prior to bioinformatics analyses, quality checks on the microarray were performed. All samples were assessed to possess good RIN quality. Unsupervised hierarchical clustering using Euclidean distance and average linkage revealed highly similar biological replicates (see Figure 3). After removing potential outliers (n = 5) as indicated in Figure 3, significance analysis of microarray (SAM) was used to select genes that had significantly different expression between sepsis and non-sepsis (fold change > 2.0 or < 0.5, false discovery rate = 0).

[00111] A set of significant differentially expressed genes in infection, mild sepsis and severe sepsis were identified through bioinformatics and pathway analyses. Finally, a heat map was generated using Java Treeview to allow visualization of the gene expression profile of each patient group.

1.5. Analytical validation of shortlisted biomarkers by qPCR

1.5.1. cDNA conversion and storage

[00112] cDNA conversion of RNA samples was performed using iScript™ cDNA Synthesis Kit (Bio-Rad) according to the manufacturer instructions.

1.5.2. Primer design and validation

[00113] Primers pairs were designed with Primer-BLAST (NCBI, NIH) and Oligo 7. All primer pairs were validated by qPCR for standard curve analysis and in three different RNA samples for melting curve before being shortlisted for additional test in patient samples.

[00114] Primer pairs were tested by SYBR Green-based qPCR. Primer pairs that were specific (consistent replicates and single peak in the qPCR melting curve analysis) with strong fold change between infection and mild sepsis subjects (fold change < 1.5) were selected. A total of 40 candidate sepsis biomarkers were shortlisted (30 up-regulated genes, 10 down-regulated genes).

[00115] Primer pairs were also tested using the standard curve method to determine the efficiencies of qPCR assays (see Table 14). PCR efficiencies were determined using the linear regression slope of template dilution series. Shortlisted biomarkers were required to have efficiency of 80-120% in the linear Ct range ($r^2 > 0.99$). All 42 primer pairs (40 shortlisted sepsis biomarkers and 2 housekeeping genes) had qPCR efficiency of greater than 80%, which indicate that a standard ddCt method for data analysis is applicable.

[00116]

1.5.3. Analysis of shortlisted biomarkers expression in patient samples by qPCR

[00117] Amplification and detection of biomarkers were performed using three systems, LightCycler 1.5 (Roche), LightCycler 480 Instrument I (Roche) and LightCycler 480 Instrument II (Roche). The LightCycler FastStart DNA MasterPlus SYBR Green I Kit (Roche) was used with LightCycler 1.5, while the LightCycler 480 SYBR Green I Master Kit (Roche) was used with LightCycler 480 Instrument I and II (Roche). For both SYBR Green kits, the final reaction volume used was 10

μ l with 1 μ M working primer concentration and 4.17 μ g cDNA template.

[00118] All reactions were performed in the following cycling conditions: 95°C for 10 minutes (initial denaturation); 40-45 cycles of 95°C for 10 seconds (denaturation), 60°C for 5 seconds (annealing) and 72°C for 25 seconds (extension) followed by melting curve analysis and cooling.

[00119] Ct values of shortlisted biomarkers were normalized against the housekeeping gene, hypoxanthine phosphoribosyltransferase 1 (HPRT1) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), to generate Δ Ct values for each gene. The relative expression differences between categories in the sepsis continuum ($\Delta\Delta$ Ct values) were also calculated. $\Delta\Delta$ Ct was then used to calculate the gene expression fold change for each gene. Formulae used are as follows:

Δ Ct = Ct biomarker - Ct housekeeping gene

$\Delta\Delta$ Ct = Ct sepsis category 1 - Ct sepsis category 2

Fold change = $2^{-\Delta\Delta$ Ct}

1.6. Development and validation of predictive model for sepsis diagnosis

[00120] A predictive model capable of classifying patients with sepsis from healthy controls that subsequently predict the severity of sepsis was developed. This was performed by training the predictive model using the gene expression (Δ Ct values from qPCR) of 46 samples (9 control, 14 SIRS, 14 mild sepsis, and 9 severe sepsis) based on the 40 significant differentially expressed genes. The predictive model was developed with two components, the classification model and regression model, dedicated to the task of diagnosing patients with sepsis, and subsequently predicting sepsis severity respectively.

[00121] Ten-fold cross validation was adopted to build and assess five classification models (random forest, decision tree, k-nearest neighbour, support vector machine and logistic regression). The model with highest ten-fold cross validation accuracy is selected (logistic regression) (see Table 4). Similarly, to predict the severity of sepsis, ten-fold cross validation was employed to train and assess different regression models (linear regression, support vector regression,

multilayer perceptron, lasso regression, elastic net regression). Likewise, the best-performing regression model in terms of ten-fold cross validation result was selected (support vector regression) (see Table 5).

[00122] Table 4 below shows the ten-fold cross validation of five data mining models.

Table 4: Ten-fold cross validation of five data mining models

Index	Method	Sensitivity (%)	Specificity (%)	Accuracy (%)
1.	RandomForest	66.7	91.9	86.96
2.	J48 (Decision tree)	55.6	89.2	82.61
3.	k-nearest neighbour (k=2)	88.9	89.2	89.13
4.	Support vector machine (poly kernel)	77.8	86.5	84.78
5.	Logistic Regression	77.8	91.9	89.13

[00123] Table 5 below shows the ten-fold cross validation of five regression models.

Table 5: Ten-fold cross validation of five regression models

Index	Method	Spearman <i>Rho</i>
1.	Linear Regression	0.8555
2.	Support Vector Regression	0.8656
3.	Multilayer Perceptron	0.8029
4.	Lasso Regression	0.8494
5.	Elastic Net Regression	0.8094

[00124] The predictive model was subjected to a blinded validation process. Twenty four blind samples were used. Prediction of patient sepsis categories was done using the established model. The results were sent to NUH for comparison to clinically assigned categories.

1.7. Development and validation of a qPCR multiplex assay for detection of sepsis

1.7.1. Assay format

[00125] Amplification and detection of biomarkers was performed using LightCycler 480 Instrument I (Roche) and LightCycler 480 Instrument II (Roche). Quantifast RT-PCR kit (Qiagen) and LightCycler® 480 Probes Master (Roche) was used. Final reaction volume was 10 μ L and 4.17 μ g of RNA or cDNA template was used.

[00126] For Quantifast RT-PCR kit, reactions were performed with the following cycling conditions: 50°C for 20 minutes (reverse transcription), 95°C for 5 minutes (initial denaturation); 40-45 cycles of 95°C for 15 seconds (denaturation), 60°C for 30 seconds (annealing and extension), followed by cooling. For LightCycler® 480 Probes Master, reactions were performed with the following cycling conditions: 95°C for 5 minutes (initial denaturation); 40-45 cycles of 95°C for 10 seconds (denaturation), 60°C for 30 seconds (annealing and extension) and 72°C for 1 second (quantification), followed by cooling.

1.7.2. Taqman probes design and validation

[00127] Taqman probes were designed using the Primer3web website (www.primer.wi.mit.edu) and Oligo 7. Autodimer was used to test for dimerization of all primer and probe combinations [1]. All primers-probe were validated in standard curve assay. Primer titration was also performed to determine the lowest primer concentration with consistent Ct value possible.

1.7.3. Validation of primers-probe combinations

[00128] Different combinations of primers-probe were tested in multiplex assay using Quantifast RT-PCR + R kit. For 3-plex assay, 0.2 μ M primers and 0.2 μ M probe for biomarkers were used while 0.4 μ M primer and 0.2 μ M probe were used for housekeeping gene. A total of 21 3-plex combinations were tested in 8 patient samples. Ct values between 3-plex and monoplex assays were compared. Only the best five 3-plex combinations (average Δ Ct difference < 1.0 for all component genes and across all sepsis continuum categories) were chosen for further validation.

1.7.4. Nascent 3-plex prototype

[00129] The best five 3-plex combinations were validated twice in 16 patient samples in Acumen Research Laboratories.

2. Results

2.1. Patient cohort

[00130] 114 subjects were involved in the study: 18 healthy controls, 3 subjects who had SIRS without infection, 30 subjects with infection, 45 subjects with mild sepsis, 15 subjects with severe sepsis and 3 subjects with cryptic shock or septic shock. The demographics and clinical data of subjects are shown in Table 6. The distribution of age, gender, and race were similar across all groups except for SIRS without infection and cryptic/septic shock categories, as both groups had low subject number. There was a male preponderance in the subjects who were recruited

[00131] The progression of patients was tracked throughout their hospital stay and for 30 days from initial date of admission to monitor for re-attendance to the ED and re-admission to hospital. There were 6 patients who returned to the ED within 30 days. 2 were for a similar infection as the initial attendance.

[00132] Table 6 below shows the subject details grouped accordingly to sepsis continuum.

Table 6: Subject details grouped according to sepsis continuum. *Numbers shown indicate the median. IQR stands for Inter Quartile Range.

Group	Total	Age*	Gender	WBC count ($\times 10^9/L$)*	Lactate (mmol/L)*	No. of ICU/HD admissions	No. of patients with hospital stay between 2-7 days	No. of Patients with hospital stay >7 days
SIRS without infection	3	29 (IQR 28- 50)	33% Male	-	-	-	-	-
Control	18	52.5 (IQR 48-64)	61% Male	-	-	-	-	-
Infection without SIRS	30	47 (IQR 38- 63)	63% Male	7.85 (IQR 7.05-10.36)	1.2 (IQR 1- 1.7)	-	14	1
Mild Sepsis	45	44.5 (IQR 31-61)	62% Male	11.3 (IQR 8.35-14.89)	1.35 (IQR 1.05-1.7)	1	19	6
Severe sepsis	15	64 (IQR 54- 70)	73% Male	11 (IQR 7.44- 16.08)	2.5 (IQR 2.17-2.7)	-	10	3
Septic shock	3	65 (IQR 49- 69)	66% Male	11.72 (IQR 11.48-14.35)	5.3 (IQR 4.1-6.5)	2	2	1

2.2. Gene expression profiling reveals potential markers for sepsis diagnosis

[00133] In order to identify potential biomarkers that are capable of distinguishing healthy controls and subjects with infection and mild sepsis, whole-genome expression microarray experiments were performed (see Material and Methods above). Significant Analysis of Microarray (SAM) analysis on the gene expression fold change relative to control was conducted to shortlist candidates from the initial ~33,000 genes on the microarray. Using a stringent thresholds of false discovery rate = 0, and fold change > 2.0 or < 0.5, 444 significantly up-regulated genes and 462 significantly down-regulated genes in sepsis were selected. Many of these identified genes such as ILR1N, IL1B, TLR1, TNFAIP6 are involved in inflammatory response ($p = 1.41 \times 10^{-5}$), immune response ($p = 1.41 \times 10^{-5}$) and wound response ($p = 1.41 \times 10^{-5}$). This is consistent with the fact that sepsis is a result of an inflammatory response to infection.

2.3. Panel of 40 genes selected as sepsis biomarkers

[00134] In order to reduce the list of 906 genes identified through SAM to a clinically feasible number for predictive model development, only the genes with the largest fold change were selected for further testing. In total, eighty five genes were tested, of which eleven were down regulated genes, and 74 were up regulated genes. After qPCR validation, a panel of 40 genes was shortlisted. The panel consists of 30 up-regulated genes and 10 down-regulated genes (see List 1 below).

[00135] HRPT1 and GAPDH were selected as the housekeeping genes for their stable expression in leukocytes [2].

[00136] List 1 below lists the gene coding sequences for each of the 30 up-regulated genes and 10 down-regulated genes. List 2 below lists the two housekeeping genes.

List 1: Gene coding sequences for each of the 30 up-regulated genes and 10 down-regulated genes

30 Up-regulated genes

1. **ACSL1**: Homo sapiens acyl-CoA synthetase long-chain family member 1 (ACSL1), mRNA. NCBI Reference Sequence: NM_001995.2 (SEQ ID NO: 1)
2. **ANXA3**: Homo sapiens annexin A3 (ANXA3), mRNA. NCBI Reference Sequence: NM_005139.2 (SEQ ID NO: 2)
3. **CYSTM1**: Homo sapiens cysteine-rich transmembrane module containing 1 (CYSTM1), mRNA. NCBI Reference Sequence: NM_032412.3 (SEQ ID NO: 3)
4. **C19orf59**: Homo sapiens chromosome 19 open reading frame 59 (C19orf59), mRNA. NCBI Reference Sequence: NM_174918.2 (SEQ ID NO: 4)
5. **CSF2RB**: Homo sapiens colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage) (CSF2RB), mRNA. NCBI Reference Sequence: NM_000395.2 (SEQ ID NO: 5)
6. **DDX60L**: Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like (DDX60L), mRNA. NCBI Reference Sequence: NM_001012967.1 (SEQ ID NO: 6)
7. **FCGR1B**: Homo sapiens Fc fragment of IgG, high affinity Ib, receptor (CD64) (FCGR1B), transcript variant 2, mRNA. NCBI Reference Sequence: NM_001004340.3 (SEQ ID NO: 7)
8. **FFAR2**: Homo sapiens free fatty acid receptor 2 (FFAR2), mRNA. NCBI Reference Sequence: NM_005306.2 (SEQ ID NO: 8)
9. **FPR2**: Homo sapiens formyl peptide receptor 2 (FPR2), transcript variant 1, mRNA. NCBI Reference Sequence: NM_001462.3 (SEQ ID NO: 9)
10. **HSPA1B**: Homo sapiens heat shock 70kDa protein 1B (HSPA1B), mRNA. NCBI Reference Sequence: NM_005346.4 (SEQ ID NO: 10)
11. **IFITM1**: Homo sapiens interferon induced transmembrane protein 1 (IFITM1), mRNA. NCBI Reference Sequence: NM_003641.3 (SEQ ID NO: 11)
12. **IFITM3**: Homo sapiens interferon induced transmembrane protein 3 (IFITM3), transcript variant 1, mRNA. NCBI Reference Sequence: NM_021034.2 (SEQ ID NO: 12)
13. **IL1B**: Homo sapiens interleukin 1, beta (IL1B), mRNA. NCBI Reference Sequence: NM_000576.2 (SEQ ID NO: 13)
14. **IL1RN**: Homo sapiens interleukin 1 receptor antagonist (IL1RN), transcript variant 1, mRNA. NCBI Reference Sequence: NM_173842.2 (SEQ ID NO: 14)
15. **LILRA5**: Homo sapiens leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 5 (LILRA5), transcript variant 1, mRNA. NCBI Reference Sequence: NM_021250.2 (SEQ ID NO: 15)
16. **LRG1**: Homo sapiens leucine-rich alpha-2-glycoprotein 1 (LRG1), mRNA. NCBI Reference Sequence: NM_052972.2 (SEQ ID NO: 16)
17. **MCL1**: Homo sapiens myeloid cell leukemia sequence 1 (BCL2-related) (MCL1), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA. NCBI Reference Sequence: NM_021960.4 (SEQ ID NO: 17)
18. **NAIP**: Homo sapiens NLR family, apoptosis inhibitory protein (NAIP), transcript variant 1, mRNA. NCBI Reference Sequence: NM_004536.2 (SEQ ID NO: 18)
19. **NFIL3**: Homo sapiens nuclear factor, interleukin 3 regulated (NFIL3), mRNA. NCBI Reference Sequence: NM_005384.2 (SEQ ID NO: 19)
20. **NT5C3**: Homo sapiens 5'-nucleotidase, cytosolic III (NT5C3), transcript variant 1, mRNA. NCBI Reference Sequence: NM_001002010.2 (SEQ ID NO: 20)
21. **PFKFB3**: Homo sapiens 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), transcript variant 1, mRNA. NCBI Reference Sequence: NM_004566.3 (SEQ ID NO: 21)
22. **PLSCR1**: Homo sapiens phospholipid scramblase 1 (PLSCR1), mRNA. NCBI Reference Sequence: NM_021105.2 (SEQ ID NO: 22)
23. **PROK2**: Homo sapiens prokineticin 2 (PROK2), transcript variant 2, mRNA. NCBI Reference Sequence: NM_021935.3 (SEQ ID NO: 23)
24. **RAB24**: Homo sapiens RAB24, member RAS oncogene family (RAB24), transcript variant 1, mRNA. NCBI Reference Sequence: NM_001031677.2 (SEQ ID NO: 24)
25. **S100A12**: Homo sapiens S100 calcium binding protein A12 (S100A12), mRNA. NCBI Reference Sequence: NM_005621.1 (SEQ ID NO: 25)

26. **SELL:** Homo sapiens selectin L (SELL), transcript variant 1, mRNA. NCBI Reference Sequence: NM_000655.4 (SEQ ID NO: 26)
27. **SLC22A4:** Homo sapiens solute carrier family 22 (organic cation/ergothioneine transporter), member 4 (SLC22A4), mRNA. NCBI Reference Sequence: NM_003059.2 (SEQ ID NO: 27)
28. **SOD2:** Homo sapiens superoxide dismutase 2, mitochondrial (SOD2), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA. NCBI Reference Sequence: NM_000636.2 (SEQ ID NO: 28)
29. **SP100:** Homo sapiens SP100 nuclear antigen (SP100), transcript variant 1, mRNA. NCBI Reference Sequence: NM_001080391.1 (SEQ ID NO: 29)
30. **TLR4:** Homo sapiens toll-like receptor 4 (TLR4), transcript variant 1, mRNA. NCBI Reference Sequence: NM_138554.4 (SEQ ID NO: 30)

10 Down-regulated genes

1. **CCL5:** Homo sapiens chemokine (C-C motif) ligand 5 (CCL5), mRNA. NCBI Reference Sequence: NM_002985.2 (SEQ ID NO: 31)
2. **CCR7:** Homo sapiens chemokine (C-C motif) receptor 7 (CCR7), mRNA. NCBI Reference Sequence: NM_001838.3 (SEQ ID NO: 32)
3. **CD3D:** Homo sapiens CD3d molecule, delta (CD3-TCR complex) (CD3D), transcript variant 1, mRNA. NCBI Reference Sequence: NM_000732.4 (SEQ ID NO: 33)
4. **CD6:** Homo sapiens CD6 molecule (CD6), transcript variant 1, mRNA. NCBI Reference Sequence: NM_006725.4 (SEQ ID NO: 34)
5. **FAIM3:** Homo sapiens Fas apoptotic inhibitory molecule 3 (FAIM3), transcript variant 1, mRNA. NCBI Reference Sequence: NM_005449.4 (SEQ ID NO: 35)
6. **FCER1A:** Homo sapiens Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide (FCER1A), mRNA. NCBI Reference Sequence: NM_002001.3 (SEQ ID NO: 36)
7. **GZMK:** Homo sapiens granzyme K (granzyme 3; tryptase II) (GZMK), mRNA. NCBI Reference Sequence: NM_002104.2 (SEQ ID NO: 37)
8. **IL7R:** Homo sapiens interleukin 7 receptor (IL7R), mRNA. NCBI Reference Sequence: NM_002185.3 (SEQ ID NO: 38)
9. **KLRB1:** Homo sapiens killer cell lectin-like receptor subfamily B, member 1 (KLRB1), mRNA. NCBI Reference Sequence: NM_002258.2 (SEQ ID NO: 39)
10. **MAL:** Homo sapiens mal, T-cell differentiation protein (MAL), transcript variant d, mRNA. NCBI Reference Sequence: NM_022440.2 (SEQ ID NO: 40)

List 2: Gene coding sequences for each of the two housekeeping genes

2 Housekeeping Genes (“HKG”)

1. **HPRT1:** Homo sapiens hypoxanthine phosphoribosyltransferase 1 (HPRT1), mRNA. NCBI Reference Sequence: NM_000194.2 (SEQ ID NO: 41)
2. **GAPDH:** Homo sapiens glyceraldehyde-3-phosphate dehydrogenase (GAPDH), mRNA. NCBI Reference Sequence: NM_002046.5 (SEQ ID NO: 42)

2.4. Each of the 40 candidate sepsis biomarkers has high sensitivity and specificity for sepsis diagnosis

[00137] The relative fold change of infection, mild and severe sepsis samples from control samples was compared by qPCR. Progressive up- or down-regulation of gene expression along the sepsis continuum was observed (see

Figure 1). This shows that the selected panel of 40 genes has potential for use in accurately differentiating subject samples along the sepsis continuum.

[00138] It is clinically important to distinguish between healthy subjects (controls) from patients with infection (infection, mild sepsis, severe sepsis). The gene panel was tested specifically for the ability to differentiate between controls and infection/mild sepsis/severe sepsis; and between controls/infection from mild sepsis/severe sepsis.

[00139] Gene expression fold changes across the sepsis continuum were greater than 1.5, and sufficiently large to be used for differentiation (see Table 15).

[00140] The predictive value of each sepsis biomarker was calculated using the Area Under Curve (AUC) of Receiver Operating Characteristic (ROC) curve for differentiation of controls from infection/mild sepsis/severe sepsis and controls/infection from mild sepsis/severe sepsis to ensure that the shortlisted biomarkers have high predictive value for the early differentiation of sepsis (see Table 16). For predictive value when differentiating control from infection/mild/severe, 3 biomarkers had > 95%, 18 biomarkers had 90-95% and 16 biomarkers had 85-90%. For predictive value when differentiating control/infection from mild/severe, 10 biomarkers had > 95%, 20 biomarkers had 90-95% and 10 biomarkers had 85-90%. p-values are < 0.01 for all biomarkers for both differentiation.

2.5. Predictive model achieved over 89% accuracy in sepsis diagnosis

[00141] A predictive model capable of differentiating between controls and subjects with infection, mild sepsis and severe sepsis was built. The model is an aggregate of two components. The first component (classification model) distinguishes patients with sepsis from controls. If the samples are identified as infection or sepsis, the second component (regression model) will predict the severity of sepsis.

[00142] The qPCR gene expression data of the earlier identified 40 differentially expressed genes from 46 samples (9 controls, 14 infection, 14 mild sepsis, and 9 severe sepsis) was used to train the first and second components of

the predictive models by using ten-fold cross validation. In each component, different models were tested and the best performing model was selected for that particular component. A logistic regression model was selected as it outperformed the other models tested. It attains a high overall accuracy of 89.13% in classifying sepsis from controls (sensitivity 77.8%, specificity 91.9%) in the ten-fold cross validation assessment.

[00143] For the second component, the support vector regression was selected to predict severity of sepsis discovered in the first component. The regression model was capable of accurately predicting the sepsis severity in 87% of the samples.

2.6. Predictive model in blinded validation achieve accuracy up to 88% in sepsis diagnosis

[00144] To further validate the applicability of our model, we performed a blinded assessment using an independent dataset not used in building the predictive models. The 24-sample independent dataset has clinically assessed 3 subjects with SIRS without infection, 4 controls, 2 infection, 12 mild sepsis, 2 severe sepsis and 1 septic shock. For assessment purposes, the subject with septic shock was classified together with severe sepsis.

[00145] The predictive model comprises two components with two purposes: diagnosis of sepsis and assessment of sepsis severity. The first component classified sepsis from controls; the selected model has a high overall accuracy of 88%, correctly diagnosing 16 out of 18 subjects with sepsis (sensitivity 94%) and accurately identifying 5 out of 7 controls (specificity 71%). More importantly, the subjects with SIRS without infection were accurately classified as control, showing that the candidate biomarkers were able to differentiate sterile SIRS from sepsis effectively.

[00146] The second component is the regression model. Despite the difficulty in predicting severity of sepsis due to the high similarity between infection and mild sepsis, the model was 82% accurate in distinguishing infection from mild sepsis or severe sepsis. This relatively low accuracy indicates the arbitrary

threshold for delineation between infection and mild sepsis in the sepsis continuum that is used to guide clinicians to risk stratify patients presenting with illness due to an infective aetiology. Infection, mild sepsis and severe sepsis induce similar inflammatory responses in varying degrees, further increasing the difficulty of making an accurate prediction using the model.

[00147] Collectively, these results (see Tables 7 and 8) demonstrate that our approach is not only feasible, but also of good accuracy diagnosing sepsis at an early stage. These results also indicate that refinement of the regression model is needed to better predict the severity of sepsis patients.

[00148] Table 7 below shows the performance of biomarker panel for classifying sepsis from control.

Table 7: Performance of biomarker panel for classifying sepsis from control

	Patient samples	Control	Sepsis
Predictions made	24	7	17
Control	6	5	1
Sepsis	18	2	16

[00149] Table 8 below shows the performance of biomarker panel for staging sepsis severity.

Table 8: Performance of biomarker panel for staging sepsis severity

	Patient samples	Infection	Mild Sepsis	Severe Sepsis
Predictions made	17	2	13	2
Infection	5	2	3	-
Mild	8	-	7	1
Severe	4	-	3	1

2.7. Development and validation of a qPCR multiplex assay for detection of sepsis

2.7.1. Development of multiplex assay

[00150] To select the most predictive genes for multiplex development, 10-fold cross validation was performed. From four different 10-fold cross validations of classification methods, 8 recurrent/overlapping genes were identified (see Figure 2). The overlapping method was chosen because it could reduce bias intrinsic to different classification models which classify data sets according to different assumptions. Concurrently, another 8 genes were selected using predictive value from comparison of control to infection/mild sepsis/severe sepsis using the ROC curve. Selected genes are shown in Table 19 below.

[00151] Three-plex combinations were designed from the most predictive genes. A total of 21 combinations of three-plex assays were screened by comparing Ct values in multiplex to monoplex of eight different patient samples (see Table 22). Of the 21 combinations, five three-plex assays had similar Ct values ($\Delta Ct < 1.0$) and were shortlisted for further validation.

2.7.2. Validation of multiplex assay using patient samples

[00152] The shortlisted five three-plex assays were tested in additional 8 patient samples. Comparison of Ct value of component genes in multiplex to monoplex assay was made (see Table 23) to determine the validity of the assay. It was observed that only S100A12/FFAR2/HPRT1 gave consistent result in patient samples from different sepsis categories. MCL1/CYSTM1/HPRT1 was less consistent. In the other three combinations, results were consistent in control

samples but not in sepsis samples. The ΔCt of the housekeeping gene, HPRT1, was higher in sepsis samples. This could be due to suppression of HPRT1 amplification by biomarkers that were highly expressed during sepsis.

3. Discussion

3.1. Biomarkers from leukocytes can be used for sepsis diagnosis

[00153] Hierarchical clustering of our microarray gene expression profiling results demonstrated significant differences in gene expression pattern of leukocytes between patients with and without infection and sepsis. Differentially expressed genes during sepsis were derived from microarray gene profiling, and a panel genes or biomarkers, in this case 40 genes, were shortlisted from the initial 33,000. The shortlisted panel of genes were validated in qPCR assay. Analytical validation using qPCR have shown that these shortlisted biomarkers were progressively dysregulated in subjects across the sepsis continuum. These results correlated to those obtained from the microarray. Gene expression changes in leukocytes can be clearly observed and potentially utilized for diagnosis and/or prognosis of sepsis and for assessing and/or predicting the severity of sepsis in a subject.

[00154] The predictive value of each gene obtained using the AUC of the ROC curve was encouraging, with scores of above 85% for every individual gene. This high predictive value of each gene suggests that the gene panel selected is capable to be utilized as early diagnostic marker. In order to fully leverage on the information from these 40 genes, a predictive model was built using the qPCR $\Delta\Delta\text{CT}$ values of all 40 genes. This predictive model was capable of accurately diagnosing 88% of the blind samples. The derived gene expression panel has been shown to be sufficiently distinct across the sepsis continuum to allow immunologic segregation of the subjects along the sepsis continuum that is based on clinical phenotypes.

3.2. Exploitation of biomarkers for sepsis diagnosis

[00155] Over 33,000 genes were examined through microarray analyses. Using SAM, 906 genes that were differentially expressed across the sepsis

continuum were identified and later further reduced to 40 genes. The expression of these 40 genes in all subjects was validated analytically through qPCR where fold change differences were used to build the predictive model.

[00156] Predictions made by the model were compared to clinical classifications and a total of 7 mismatched predictions were found. Of the 7 mismatched predictions, 4 of them made no difference to patient management, while 3 could have resulted in adverse outcomes. Despite the small number of SIRS without infection subjects, the model was able to correctly classify both subjects in the blind sample testing. However, further refinement of the model through a subsequent clinical validation phase will have to be carried out to increase its specificity and sensitivity. The panel of genes could potentially be further decreased without sacrificing its accuracy to improve cost efficiency and reproducibility. The use of a larger data set to train the predictive model is paramount to this mission. Other improvements to the system, such as the use of new housekeeping genes to ensure that the baseline used for comparison is stable and able to account for differences in age and gender of the individuals.

3.3. *Prototyping of diagnostic kit*

[00157] The qualitative gene expression data obtained can be used for multiple applications, including the differentiation of infected and non-infected patients, differentiation of sepsis and non-sepsis patients, and staging severity of sepsis, through the use of different predictive models. Existing data can be merged with new data from future studies for use in new predictive model building. Should it be desirable, new genes can be selected from the microarray data. This could be useful if sufficient information on patient disease progression could be obtained and new genes specifically for use in classifying patient disease prognosis were to be identified. Thus, there is unparalleled flexibility to exploit the data obtained from this study.

[00158] Currently, RNA from leukocytes is used as the template for the prototype development. However, starting material for the final prototype may be determined by multiple factors such as processing time and complexity, sensitivity and stability of the assay, equipment available in hospitals, and time taken for

sample preparation will have to be considered.

3.4. *Clinical utility of diagnostic kit*

[00159] Currently, there is no gold standard for diagnosis of sepsis. Most initial tests rely on positive blood cultures. There are several major drawbacks for relying on blood cultures including the lengthy time required to obtain definitive results (24 to 72 hours), large volume of blood required (usually 20ml to 40ml) and false positive rates (0.6% to 10%) [3,4]. Several pathogen-based molecular diagnostic kits have been made commercially available to circumvent this problem, for example, FilmArray® Blood Culture Identification panel (BioFire Diagnostics Inc.). However, this method only identifies the pathogen (and its by-products e.g. endotoxins) that has incited the host inflammatory response and allows targeted anti-microbial therapy to be instituted but does not indicate the collateral damage caused by the over-exuberant host inflammatory response or the severity of sepsis.

[00160] The limitation of blood cultures lies also in false negative results which may be caused by low bacterial concentrations in blood, insufficient blood extracted into the culture bottles, presence of fastidious organisms or the use of antibiotics prior to sample collection. Data from NUH ED between 2007 and 2012 showed a true positive blood culture rate of only 21.4% for patients above 65 years old.

[00161] The proposed diagnostic kit utilising qPCR assays for the host response in the form of gene expression changes due to infection/sepsis complements the pathogen-based molecular techniques described above. The ability to ascertain a host response for early diagnosis precedes the utilisation of pathogen identification to allow more rapid and accurate management of patients who do not manifest sepsis clinically initially but who may deteriorate later. The pillars of sepsis management including source control, early haemodynamic resuscitation and support, and ventilator support can then be instituted early to improve patient outcomes. The estimated 3 hours required by the gene expression diagnostic kit presents an opportunity for front line doctors such as emergency physicians to make rapid informed decisions for triage and right-siting

of care in the hospital.

4. *Supplementary Methods*

4.1. *Gene expression profiling*

4.1.1. *Quality control for comparable microarray analysis*

[00162] Quality control (QC) for microarray hybridization was performed. Control metrics used were hybridization controls for hybridization procedure, low stringency tests for washing temperature, high stringency tests for Cy3 binding, negative controls for non-specific hybridization, gene intensity tests for integrity of samples and amount of hybridization and finally signal distribution analysis to detect outliers.

4.2. *Analytical validation of shortlisted biomarkers by qPCR*

4.2.1. *Primers design and validation*

[00163] The National Centre for Biotechnology Information (NCBI) nucleotide database was used to obtain the coding sequence for each of our selected genes. Primer-BLAST was then run to get 20 different primer pairs for each gene. The parameters used were: 200 bp maximum PCR product size; 20 primer pairs returned; primer melting temperature of minimum 59°C, maximum 61°C and maximum difference of 2°C. Each pair was then tested for stability and usage in silico using Oligo 7. Top two primer pairs that score more than 700 points were selected for use in qPCR.

[00164] Before starting the experiments, each primer pair was tested to check their quality. New primers were tested with three different samples by qPCR. The melting curve was checked to verify that there are no side products or primer dimers. Additionally, standard curve analysis was done to calculate the correlation coefficient (r^2) and the efficiency (E) of the primer pairs. The formula used to calculate efficiency is as follows:

$$E = [-1 + 10(1/\text{slope})] \times 100\%$$

[00165] The slope was calculated from the standard curve. The validated primer pairs were then used for analytical validation (see Table 9).

[00166] Table 9 below shows the list of primers used.

Table 9: List of primers used

Name	Forward primer	Reverse primer
ACSL1	GCTCTCGGAAACCAGACCAA	AAGCCCTTCTGGATCAGTGC
ANXA3	GTTGGACACCGAGGAACAGT	CGCTGTGCATTTGACCTCTC
C19ORF59	AACTCCGTACAAGCATGCGA	GGCATTCTTCTGCAGCACCTC
CSF2RB	CCACGGCCAATACATCGTCT	TTGGTCACGTTGAGGGATGG
CYSTM1	ACCCTACCCACCTCCTCAAG	AGGTGGATGGTCCTAGCTCA
DDX60L	CTGAGGACTGCACGTATGCT	TGTAAATCGCACTCGCGGTA
FCGR1B	TTGAGGTGTCATGCGTGGA	TGCCTGAGCAATGGTAGGTG
FFAR2	GGAGTGATTGCAGCTCTGGT	GACCTGCTCAGTCGTGTTCA
FPR2	GGCTACACTGTTCTGCGGAT	CACCCAGATCACAAGCCCAT
HSPA1B	CCTGTTTGAGGGCATCGACT	TCGTGAATCTGGGCCTTGTC
IFITM1	CAACATCCACAGCGAGACCT	TCGCCAACCATCTTCCTGTC
IFITM3	CATGTCGTCTGGTCCCTGTT	GTCGCCAACCATCTTCCTGT
IL1B	ACCACTACAGCAAGGGCTTC	ATCGTGACATAAGCCTCGT
IL1RN	CCAGCAAGATGCAAGCCTTC	GACTTGACACAGGACAGGCA
LILRA5	GATTCCGGTCTCAGGAGCAG	GAATCCCAAGGACCACCAGG
LRG1	CAGACAGCGACCAAAAAGCC	ATTTCCGGCAGGTGGTTGACA
MCL1-V1	AACTGGGGCAGGATTGTGAC	CCCATCCAGCCTCTTTGTT
NAIP	CCTCACGAGACTCCCATAGA	CGCAAGTCTAGCCTCCTCTT
NFIL3	AGGCCACGCAAAAACCTTCC	TGATGCCAGTGCTCCGATTT
NT5C3	ACAACATAGCATCCCCGTGT	TGAGCACCCCAAGTTTCATCA
PFKFB3	AGTGCAGAGGAGATGCCCTA	ATTCCACACGGCAGCCATAA
PLSCR1	CGCCACAGCCTCCATTAAAC	TCCGCTGCAAAAGTAAACCCT
PROK2	AGGACTCCCAATGTGGTGGA	TCCCAGTTTGCCCATAGGTG
RAB24	TGCCATCGTCTGCTATGACC	CGCAGTTCCTTCACCCAGAA
S100A12	CGGAAGGGGCATTTTGACAC	TGGTGTTTGCAAGCTCCTTTG
SELL	GAAGTGGGGAGATGGTGAGC	TAGTTTGTGGCAGGCGTCAT
SLC22A4	GTTCAGCCAGGACGTCTACC	GCACCTTCCAGTTGTCCTCA
SOD2	AAACCTCAGCCCTAACGGTG	GAAACCAAGCCAACCCCAAC
SP100	CTTGCTCACGACCCAGATT	GGAGCCTTCTCACCATGCTT
TLR4	CATTGGTGTGTCGGTCCTCA	CCAGTCCTCATCCTGGCTTG
MAL	CTTGCCCGACTTGCTCTTCA	AGAACACCGCATGGACCAC
CCR7	CTTGTCATCATCCGCACCCT	GAGCTCACAGGTGCTACTGG
GZMK	GTTACTACAACGGCGACCCT	AGATTCCAGGCTTTGTGGCA
FCER1A	CCAGATGGCGTGTTAGCAGT	TGAAAGGCTGCCATTGTGGA
FAIM3	GAGCCATCATGGGAAGAGCA	GAGTGGTGAAGTGGAGGGAC
CD3D	GTCTATCAGCCCCTCCGAGA	ACTTGTTCCGAGCCCAAGTTT
CD6	ATGAGGAGGTCCAGCAAAGC	AGGTGCTCGACTCACTGTTG
KLRB1	TGAAACTTAGCTGTGCTGGGA	CTCTCGGAGTTGCTGCCAAT
IL7R	CCAACCGGCAGCAATGTATG	AGGATCCATCTCCCCTGAGC
CCL5	CAGTCGTCTTTGTCACCCGA	GTTGATGTAATCCCGAACCCA
HPRT1	CCTGGCGTCGTGATTAGTGA	CGAGCAAGACGTTCAAGTCTT
GAPDH	CCTGGCGTCGTGATTAGTGA	CTCGCTCCTGGAAGATGGTG

4.3. Development and validation of a qPCR multiplex assay for detection of sepsis

4.3.1. Taqman probes design and validation

[00167] Taqman probes were designed using the Primer3web website (www.primer.wi.mit.edu) with the following parameters: Probe size was between 18-27bp; probe melting temperature (T_m) 65-73°C; GC content 30-80%. Each probe was then tested for stability and usage in silico using Oligo 7. Autodimer was used to test for primer-probe and probe-probe and primer-primer dimerization for all primer and probe combinations [1] (see Table 10).

[00168] Table 10 below shows the list of primers-probe combinations.

Table 10: List of primers-probe combinations

Name	Forward primer	Reverse primer	Probe	Fluorophore
CYSTM1	ACCCTACCCACCT CCTCAAG	AGGTGGATGGTCC TAGCTCA	TACGGCTGGCAGG GTGGACC	FAM
IFITM1	CAACATCCACAGC GAGACCT	TCGCCAACCATCTT CCTGTC	CCGTGCCCCGACCA TGTCGTCTGGTCC C	FAM
FFAR2	GGAGTGATTGCAG CTCTGGT	GACCTGCTCAGTC GTGTTCA	TGTCCTTTGGTCAC TGCACCATCGTGA	FAM
SP100	CTTGCTCACGACC CCAGATT	GGAGCCTTCTCAC CATGCTT	AGTGAGGAGGAGG CGCCCGC	HEX
IFITM3	CATGTCGTCTGGT CCCTGTT	GTCGCCAACCATC TTCCTGT	ACCCCTGCTGCCT GGGCTTCA	HEX
SOD2	AAACCTCAGCCCTA ACGGTG	GAAACCAAGCCAA CCCCAAC	ACGGCTGCATCTG TTGGTGTCCAAGG C	HEX
CSF2RB	CCACGGCCAATAC ATCGTCT	TTGGTCACGTTGA GGGATGG	GCTCAGTGAACAT CCAGATGGCCCC	Cy5
PROK2	AGGACTCCCAATG TGGTGGA	TCCCAGTTTGCCCA TAGGTG	TGTGCTGTGCTGT CAGTATCTGGGT	Cy5
HPRT1	TCAGGCAGTATAAT CCAAAGATGGT	AGTCTGGCTTATAT CCAACACTTCG	CAAGCTTGCTGGT GAAAAGGACCCC	Texas Red
HSPA1B	CCTGTTTGAGGGC ATCGACT	TCGTGAATCTGGG CCTTGTC	AGCACCCCTGGAGC CCGTGGA	Cy5
S100A12	CGGAAGGGGCATT TTGACAC	TGGTGTGTTGCAAG CTCCTTTG	AGGGTGAGCTGAA GCAGCTGCTTACA	LC Cyan 500
MCL1	AACTGGGGCAGGA TTGTGAC	CCCATCCCAGCCT CTTTGTT	TCGTAAGGACAAAA CGGGACTGGCT	LC Cyan 500

[00169] Primer-probe mix was first tested in standard curve assay using serial dilution of template RNA on two different kits: QuantiFast® Multiplex RT-PCR Kit (Qiagen) and LightCycler® 480 Probes Master (Roche). Sets were validated to ensure that the probe is compatible with primer pairs: the amplification efficiency is within the range of 80-120% and fold change is linear across tested Ct

range.

[00170] Next, primer titration from 0.4-0.05 μM at 0.05 μM steps was performed to determine the lowest primer concentration possible while maintaining Ct value from the recommended primer concentration of 0.4 μM .

5. *Supplementary Results*

5.1. *RNA sample preparation*

5.1.1. *RNA quality and quantity*

[00171] The average RNA concentration and ratio for 260/280 and 260/230 acquired for all RNA samples are found. The RNA quality and quantity acquired had concentration > 50 ng/uL, 280/260 ratio > 2.0, and 260/230 ratio > 1.7, showing that good yield was obtained from RNA extraction and RNA samples used were not contaminated with proteins and carbohydrates.

5.2. *Gene expression profiling*

5.2.1. *RNA quality and concentration for microarray*

[00172] RNA quality and integrity were tested with Bioanalyzer before being used for microarray experiments. RNA integrity number (RIN) for all samples used in microarray were > 7. Electrophoretic runs showed that sharp bands of RNA were present. Results confirmed that RNA samples used in microarray had high integrity and were not degraded.

5.2.2. *Quality control for microarray hybridization*

[00173] Quality control (QC) for microarray hybridization was also performed. Both the pilot (see Table 12) and second microarray (see Table 13) runs passed all quality control tests.

[00174] Table 12 below shows the summary of array quality controls for pilot microarrays.

Table 12: Summary of array quality controls for the first batch of microarray

Control Metric	Descriptions	Results
Hybridization Controls	To QC hybridization procedures	Pass ; Signals of hybridization control probes met expected values High > Medium > Low
Low Stringency	To QC hybridization temperature and high temperature washing	Pass ; Perfect Match probes generated higher signals than the Mismatch probes
Biotin and High Stringency	To QC streptavidin-Cy3 staining	Pass ; Biotin-conjugated control probes showed high signals of Cy3 staining
Negative Controls	To QC non-specific hybridization	Pass ; Background signals and noise were at low levels
Gene Intensity	To QC integrity of the biological samples and variations in the amount of samples hybridized	Acceptable ; Signals of genes were higher than background and met the expected Housekeeping > All Genes; Slight variations in the amount of samples hybridized
Signal Distribution (Box Plot)	Visualization of inter-array variations to identify outliers	Pass ; No outliers identified; Slight variations observed as expected

[00175] Table 13 below shows the summary of array quality controls for the second batch of microarray.

Table 13: Summary of array quality controls for second microarray

Control Metric	Descriptions	Results
Hybridization Controls	To QC hybridization procedures	Pass ; Signals of hybridization control probes met expected values High > Medium > Low
Low Stringency	To QC hybridization temperature and high temperature washing	Pass ; Perfect Match probes generated higher signals than the Mismatch probes
Biotin and High Stringency	To QC streptavidin-Cy3 staining	Pass ; Biotin-conjugated control probes showed high signals of Cy3 staining
Negative Controls	To QC non-specific hybridization	Pass ; Background signals and noise were at low levels
Gene Intensity	To QC integrity of the biological samples and variations in the amount of samples hybridized	Acceptable ; Signals of genes were higher than background and met the expected Housekeeping > All Genes; Slight variations in the amount of samples hybridized
Signal Distribution (Box Plot)	Visualization of inter-array variations to identify outliers	Pass ; No outliers identified; Slight variations observed as expected

5.3. Analytical validation of shortlisted genes by qPCR

5.3.1. Primer test and validation

[00176] Primer pairs were also tested with the standard curve method to determine the efficiencies of qPCR assays (see Table 14). PCR efficiencies were determined using the linear regression slope of template dilution series. Shortlisted biomarkers were required to have efficiency of 80-120% in the linear Ct range ($r^2 > 0.99$). Among the 41 primer pairs (40 shortlisted sepsis biomarkers and 1 housekeeping gene), none had qPCR efficiency of $< 80\%$. However, 11 primer pairs had efficiency $> 120\%$. Despite having $> 120\%$ efficiency, these primer pairs were still used to study gene expression changes during sepsis since no false products were detected in the melting curve.

[00177] Table 14 below shows the efficiency and linear Ct range primer pairs of shortlisted sepsis biomarkers.

Table 14: Efficiency and linear Ct range primer pairs of shortlisted sepsis biomarkers

No.	Gene name	Efficiency	r ²	Linear Ct range	
1.	IL1RN	95%	0.9974	20.57	27.49
2.	SLC22A4	109%	-	30.07	33.19
3.	PLSCR1	95%	0.9997	21.63	28.53
4.	ANXA3	93%	0.9987	21.41	28.40
5.	LRG1	87%	0.9997	27.34	34.69
6.	C19ORF59	91%	0.9860	25.71	32.84
7.	ACSL1	107%	0.9969	24.18	30.52
8.	PFKFB3	96%	1.0000	21.91	28.74
9.	FFAR2	124%	0.9994	25.54	31.24
10.	FPR2	125%	0.9990	24.6	33.13
11.	HSPA1B	127%	0.9983	23.12	28.73
12.	NT5C3	137%	0.9944	23.70	29.03
13.	DDX60L	140%	0.9922	23.89	29.16
14.	SELL	109%	0.9993	22.02	31.44
15.	IFITM1	133%	0.9945	20.21	28.56
16.	RAB24	134%	0.9989	25.73	33.93
17.	MCL1-V1	141%	0.9984	20.48	25.72
18.	PROK2	117%	0.9995	21.89	27.84
19.	LILRA5	98%	1.0000	22.68	29.42
20.	TLR4	122%	0.9990	22.73	28.50
21.	NFIL3	123%	0.9979	22.53	28.27
22.	IL1B	105%	0.9976	23.29	29.70
23.	CYSTM1	110%	0.9991	21.47	27.69
24.	CSF2RB	122%	0.9998	21.83	27.95
25.	IFITM3	117%	0.9990	16.11	22.07
26.	SOD2	112%	0.9981	19.43	25.54
27.	FCGR1B	115%	0.9994	21.08	27.09
28.	S100A12	96%	0.9997	18.23	25.05
29.	SP100	100%	0.9983	21.76	28.42
30.	NAIP	86%	0.9979	21.17	28.61
31.	MAL	111%	-	31.68	34.76
32.	CCR7	99%	0.9993	26.99	33.66
33.	GZMK	85%	0.9918	27.815	35.32
34.	FCER1A	97%	0.9990	29.205	36.00
35.	FAIM3	100%	0.9997	26.925	33.55
36.	CD3D	91%	0.9992	26.935	34.08
37.	CD6	82%	0.9946	28.325	36.03
38.	KLRB1	99%	0.9938	27.865	34.55
39.	IL7R	84%	0.9802	27.14	34.70
40.	CCL5	104%	0.9999	25.02	31.47
41.	HRPT1	106%	0.9974	26.26	32.62

5.3.2. Diagnostic performance of shortlisted genes

[00178] Figure 1 shows the relative fold change of infection, mild and severe sepsis samples over control by qPCR. (A) 30 up-regulated genes; and (B) 10 down-regulated genes.

[00179] Table 15 below shows the fold change between control versus infection and infection versus mild sepsis. *C* – control, *I* – infection, *M*- mild.

Table 15: Fold change between control versus infection and infection versus mild sepsis *C* – control, *I* – infection, *M*- mild.

No.	Gene name	Fold change Control versus Infection	Fold change Infection versus Mild Sepsis	No.	Gene name	Fold change Control versus Infection	Fold change Infection versus Mild Sepsis
1.	IL1RN	3.18	5.09	21.	NFIL3	2.83	3.81
2.	SLC22A4	1.14	5.47	22.	IL1B	4.11	5.59
3.	PLSCR1	3.16	8.09	23.	CYSTM1	4.54	6.31
4.	ANXA3	4.57	7.77	24.	CSF2RB	2.84	4.19
5.	LRG1	4.64	5.21	25.	IFITM3	3.39	4.94
6.	C19ORF59	2.58	7.60	26.	SOD2	5.21	4.02
7.	ACSL1	3.62	7.69	27.	FCGR1B	3.76	6.07
8.	PFKFB3	2.27	5.21	28.	S100A12	4.05	3.47
9.	FFAR2	5.10	3.98	29.	SP100	1.41	3.06
10.	FPR2	2.62	2.97	30.	NAIP	2.01	3.58
11.	HSPA1B	1.42	3.99	31.	MAL	1.61	4.92
12.	NT5C3	1.78	4.39	32.	CCR7	1.60	2.59
13.	DDX60L	2.17	5.84	33.	GZMK	2.42	2.74
14.	SELL	2.07	3.95	34.	FCER1A	2.80	3.07
15.	IFITM1	2.69	5.79	35.	FAIM3	1.97	2.72
16.	RAB24	1.98	3.38	36.	CD3D	1.63	2.92
17.	MCL1-V1	1.50	3.06	37.	CD6	1.38	3.04
18.	PROK2	4.79	5.80	38.	KLRB1	1.86	2.95
19.	LILRA5	1.83	3.92	39.	IL7R	1.57	2.39
20.	TLR4	2.51	3.28	40.	CCL5	1.94	2.85

[00180] Table 16 below shows the predictive value (Area Under Curve; AUC), standard deviation and *p*-value of biomarker panel for control versus infection/mild sepsis/severe sepsis and control/infection versus mild sepsis/severe sepsis.

Table 16: Predictive value (Area Under Curve; AUC), standard deviation and p-value of biomarker panel for control versus infection/mild sepsis/severe sepsis and control/infection versus mild sepsis/severe sepsis.

No.	Gene name	Control vs Infection/Mild/Severe			Control/Infection vs Mild/Severe		
		AUC	SD	p-value	AUC	SD	p-value
1.	IL1RN	90.1%	4.5%	0.0002	90.2%	5.2%	< 0.0001
2.	SLC22A4	85.6%	5.5%	0.0010	90.6%	4.7%	< 0.0001
3.	PLSCR1	90.4%	4.4%	0.0002	95.7%	3.1%	< 0.0001
4.	ANXA3	92.8%	3.8%	< 0.0001	95.1%	2.9%	< 0.0001
5.	LRG1	93.1%	3.8%	< 0.0001	93.3%	3.4%	< 0.0001
6.	C19ORF59	91.6%	4.7%	0.0001	96.4%	2.3%	< 0.0001
7.	ACSL1	91.7%	4.1%	0.0001	94.7%	3.1%	< 0.0001
8.	PFKFB3	88.3%	4.9%	0.0004	94.7%	2.9%	< 0.0001
9.	FFAR2	94.6%	3.3%	< 0.0001	89.1%	5.0%	< 0.0001
10.	FPR2	90.1%	4.6%	0.0002	89.3%	4.8%	< 0.0001
11.	HSPA1B	82.0%	7.0%	0.0032	88.1%	5.5%	< 0.0001
12.	NT5C3	87.1%	5.2%	0.0006	91.6%	4.1%	< 0.0001
13.	DDX60L	88.0%	5.2%	0.0005	95.8%	2.9%	< 0.0001
14.	SELL	88.9%	4.9%	0.0003	91.5%	4.7%	< 0.0001
15.	IFITM1	88.6%	4.8%	0.0004	92.4%	4.6%	< 0.0001
16.	RAB24	89.8%	4.7%	0.0002	93.6%	3.5%	< 0.0001
17.	MCL1-V1	88.1%	5.2%	0.0004	95.0%	3.0%	< 0.0001
18.	PROK2	94.0%	3.5%	< 0.0001	95.7%	2.6%	< 0.0001
19.	LILRA5	87.7%	5.1%	0.0005	95.8%	2.6%	< 0.0001
20.	TLR4	92.2%	4.1%	0.0001	92.6%	3.6%	< 0.0001
21.	NFIL3	92.2%	4.1%	0.0001	95.1%	2.8%	< 0.0001
22.	IL1B	92.5%	4.0%	< 0.0001	93.3%	3.5%	< 0.0001
23.	CYSTM1	96.9%	2.3%	< 0.0001	97.9%	1.6%	< 0.0001
24.	CSF2RB	94.0%	3.4%	< 0.0001	93.8%	3.4%	< 0.0001
25.	IFITM3	95.5%	3.0%	< 0.0001	96.0%	2.4%	< 0.0001
26.	SOD2	94.9%	3.1%	< 0.0001	91.1%	4.1%	< 0.0001
27.	FCGR1B	96.3%	2.6%	< 0.0001	90.0%	4.4%	< 0.0001
28.	S100A12	94.7%	3.7%	< 0.0001	90.2%	4.4%	< 0.0001
29.	SP100	90.4%	4.4%	0.0002	97.7%	1.7%	< 0.0001
30.	NAIP	89.3%	4.7%	0.0003	91.1%	4.2%	< 0.0001
31.	MAL	86.6%	5.6%	0.0007	94.0%	3.3%	< 0.0001
32.	CCR7	86.2%	6.1%	0.0009	88.7%	4.9%	< 0.0001
33.	GZMK	93.4%	4.1%	< 0.0001	88.7%	5.0%	< 0.0001
34.	FCER1A	89.8%	4.9%	0.0002	85.8%	5.5%	< 0.0001
35.	FAIM3	91.9%	4.2%	0.0001	92.5%	3.7%	< 0.0001
36.	CD3D	89.8%	4.9%	0.0002	92.1%	4.2%	< 0.0001
37.	CD6	84.5%	5.9%	0.0015	92.6%	4.0%	< 0.0001
38.	KLRB1	88.6%	5.6%	0.0004	89.4%	4.8%	< 0.0001
39.	IL7R	81.7%	6.9%	0.0035	89.5%	4.5%	< 0.0001
40.	CCL5	89.6%	5.3%	0.0003	88.2%	5.3%	< 0.0001

5.3.3. Derivation of predictive model for differentiation of sepsis categories

[00181] Weights were given to each gene to generate the logistic regression index were shown (see Table 17). The algorithm used for classifying blind patient

sample during clinical validation will be:

$$\text{Logistic regression index} = \sum (dC_i \cdot w) + I$$

dC_i - gene cycle threshold normalized to housekeeping gene

w - weight

I - intercept

For healthy control samples, logistic regression index ≥ 0

For infected/sepsis samples, logistic regression index < 0

[00182] Table 17 below shows the weights for each gene and intercept from logistic regression model.

Table 17: Weights for each gene and intercept from logistic regression model.

No.	Gene name	Weight	No.	Gene name	Weight
1.	IL1RN	2.9035	21.	NFIL3	-5.9539
2.	SLC22A4	-1.9025	22.	IL1B	-0.9397
3.	PLSCR1	6.3155	23.	CYSTM1	8.7944
4.	ANXA3	-2.1455	24.	CSF2RB	-0.6782
5.	LRG1	-0.4864	25.	IFITM3	12.506
6.	C19ORF59	0.5169	26.	SOD2	11.0719
7.	ACSL1	-2.2421	27.	FCGR1B	9.6114
8.	PFKFB3	-4.0446	28.	S100A12	9.3856
9.	FFAR2	-1.5183	29.	SP100	7.6691
10.	FPR2	-7.6375	30.	NAIP	-0.0011
11.	HSPA1B	-1.4681	31.	MAL	1.7855
12.	NT5C3	-2.9469	32.	CCR7	-6.1928
13.	DDX60L	-5.1756	33.	GZMK	-1.4079
14.	SELL	-3.2046	34.	FCER1A	-7.0497
15.	IFITM1	6.8869	35.	FAIM3	-11.3155
16.	RAB24	-1.6036	36.	CD3D	8.0665
17.	MCL1-V1	-16.5876	37.	CD6	15.9739
18.	PROK2	3.3069	38.	KLRB1	-1.2603
19.	LILRA5	-9.2405	39.	IL7R	0.8408
20.	TLR4	-1.2054	40.	CCL5	3.4355
	Intercept	109.3536			

[00183] Weights were given to each gene to generate the support vector regression index were shown (see Table 18). The algorithm used for classifying blind patient sample during clinical validation will be:

$$\text{Support vector regression index} = \sum (dC_i \cdot w) + I$$

dC_i - gene cycle threshold normalized to housekeeping gene

w - weight

I - intercept

For infection samples, support vector regression index ≥ 1.41

For mild sepsis samples, support vector regression index $1.41 \geq x < 3.52$

For severe sepsis samples, support vector regression index < 3.52

[00184] Table 18 below shows the weights for each gene and intercept from support vector regression model.

Table 18: Weights for each gene and intercept from support vector regression model.

No.	Gene name	Weight	No.	Gene name	Weight
1.	IL1RN	0.227	21.	NFIL3	0.1661
2.	SLC22A4	0.2338	22.	IL1B	0.0219
3.	PLSCR1	0.1354	23.	CYSTM1	-0.0325
4.	ANXA3	0.0052	24.	CSF2RB	0.2387
5.	LRG1	0.0987	25.	IFITM3	0.1498
6.	C19ORF59	-0.2757	26.	SOD2	0.1162
7.	ACSL1	-0.145	27.	FCGR1B	0.1017
8.	PFKFB3	0.0545	28.	S100A12	-0.28
9.	FFAR2	-0.0471	29.	SP100	-0.7538
10.	FPR2	-0.0067	30.	NAIP	-0.1359
11.	HSPA1B	-0.4868	31.	MAL	0.0864
12.	NT5C3	-0.3787	32.	CCR7	0.0372
13.	DDX60L	-0.0569	33.	GZMK	-0.0396
14.	SELL	0.1356	34.	FCER1A	0.0254
15.	IFITM1	0.4329	35.	FAIM3	0.0914
16.	RAB24	-0.1011	36.	CD3D	0.2472
17.	MCL1-V1	-0.2838	37.	CD6	0.4069
18.	PROK2	0.2847	38.	KLRB1	-0.0664
19.	LILRA5	-0.0464	39.	IL7R	0.1173
20.	TLR4	-0.1839	40.	CCL5	-0.0715
	Intercept	0.635			

5.4. Development and validation of a qPCR multiplex assay for detection of sepsis

[00185] **Figure 2** shows the most predictive genes identified from overlap of four different classification methods.

[00186] Table 19 below shows the list of top eight predictive genes from two different selection methods.

Table 19: List of top eight predictive genes from two different selection methods

No.	ROC predictive value	No.	Overlap of classification models
1.	CYSTM1	1.	S100A12
2.	FCGR1B	2.	SP100
3.	IFITM3	3.	HSPA1B
4.	SOD2	4.	CYSTM1
5.	S100A12	5.	C19ORF59
6.	FFAR2	6.	CD6
7.	PROK2	7.	MCL-V1
8.	CSF2RB	8.	FCER1A

[00187] Primers-probe was tested with the standard curve method to confirm that primers-probe can produce amplification curves and to determine the efficiencies of qPCR assays. PCR efficiencies were determined using the linear regression slope of template dilution series. Similar to qPCR using SYBR Green format, primers-probe need to have efficiency of 80-120% in the linear Ct range ($r^2 > 0.99$).

[00188] Primers-probe for 12 biomarkers and one housekeeping were designed. Primers-probe of two genes failed to produce amplification curves. Of the 4 housekeeping primer probes, one was chosen for most consistent result. All probes which worked have acceptable efficiency (80-120%) and linear in tested Ct range (see Table 20).

[00189] Table 20 below shows the efficiency and linear Ct range primers-probe of tested sepsis biomarkers.

Table 20: Efficiency and linear Ct range primers-probe of tested sepsis biomarkers

No.	Gene name	Efficiency	r ²	Ct range	
1.	CYSTM1	96%	0.9685	26.65	37.32
2.	FFAR2	116%	0.9991	24.61	30.61
3.	IFITM1	121%	0.9800	20.97	29.49
4.	HPRT1	85%	0.9980	28.98	36.48
5.	CSF2RB	113%	0.9960	23.48	32.44
6.	PROK2	117%	0.9990	23.85	29.80
7.	SP100	105%	0.9980	25.53	35.06
8.	SOD2	121%	0.9892	23.57	29.37
9.	IFITM3	108%	0.9993	20.69	26.96
10.	S100A12	75%	0.9984	21.81	34.25
11.	MCL1	82%	0.9962	19.80	31.26
12.	HSPA1B	82%	0.9964	23.73	35.46

[00190] Primer titration was performed to reduce the primer concentration used for highly abundant genes (see Table 21). Reduced primer concentration should not be affecting Ct value compared to the recommended starting working concentration of 0.4 μ M. Reducing primer concentration will limit the effect of amplification suppression of highly abundant genes on low abundant genes through qPCR reactant competition and depletion. Since, possible minimum final primer concentration ranged from 0.20 to 0.05 μ M, 0.2 μ M was selected as the final primer concentration for all biomarkers. Final primer concentration for low abundance housekeeping gene was maintained at 0.4 μ M.

[00191] Table 21 below shows the efficiency and linear Ct range primers-probe of tested sepsis biomarkers.

Table 21: Efficiency and linear Ct range primers-probe of tested sepsis biomarkers.

	Slope	Titration	Minimum
HPRT1	2.01	Ct up	-
CYSTM1	0.61	Stable	0.10
FFAR2	0.24	Stable	0.05
SP100	-0.29	Stable	0.05
SOD2	-1.66	Ct down	0.15
IFITM3	-0.08	Stable	0.10
IFITM1	1.67	Ct up	0.10
CSF2RB	4.18	Ct up	0.10
PROK2	-3.19	Ct down	0.20

[00192] Table 22 below shows the tested 3-plex combinations.

Table 22: Tested 3-plex combinations

No.	Combinations
1.	CYSTM1/SP100/HPRT1
2.	CYSTM1/SOD2/HPRT1
3.	CYSTM1/IFITM3/HPRT1
4.	FFAR2/SP100/HPRT1
5.	FFAR2/SOD2/HPRT1
6.	FFAR2/IFITM3/HPRT1
7.	IFITM1/SP100/HPRT1
8.	IFITM1/SOD2/HPRT1
9.	IFITM1/IFITM3/HPRT1
10.	MCL1/CYSTM1/HPRT1
11.	MCL1/FFAR2/HPRT1
12.	MCL1/IFITM1/HPRT1
13.	MCL1/SP100/HPRT1
14.	MCL1/SOD2/HPRT1
15.	MCL1/IFITM3/HPRT1
16.	S100A12/CYSTM1/HPRT1
17.	S100A12/FFAR2/HPRT1
18.	S100A12/IFITM1/HPRT1
19.	S100A12/SP100/HPRT1
20.	S100A12/SOD2/HPRT1
21.	S100A12/IFITM3/HPRT1

[00193] Table 23 below shows the number of samples with Ct difference between multiplex and monoplex assays of more than 1.0 for shortlisted 3-plex combinations.

Table 23: Number of samples with Ct difference between multiplex and monoplex assays of more than 1.0 for shortlisted 3-plex combinations

Combination	Gene 1 Gene 2 Gene 3	CYSTM1/ SOD2/ HPRT1	MCL1/ CYSTM1/ HPRT1	FFAR2/ SOD2/ HPRT1	S100A12/ FFAR2/ HPRT1	S100A12/ SOD2/ HPRT1
In control samples	Gene 1	0	0	0	0	0
	Gene 2	0	1	1	0	0
	Gene 3	0	1	0	0	0
In sepsis samples	Gene 1	0	0	0	0	0
	Gene 2	0	0	0	0	0
	Gene 3	6	2	0	5	5

[00194] **Figure 3** shows an unsupervised hierarchical clustering heatmap of the sepsis data panel (red = high expression, green = low expression). Row is gene, and column is sepsis/control sample. Highlighted samples are potential outliers.

6. Further Examples

[00195] To further demonstrate utilization of biomarker set or biomarker panel a subsequent cohort of 151 patients' samples was utilized. The sub-classification of the 151 samples is as follows: 36 controls, 6 SIRS without infection, 24 infection without SIRS, 67 mild Sepsis, 12 severe sepsis and 6 septic shock/cryptic shock. Examples in the following paragraphs are based on this sample set.

[00196] Table 24 below shows the predictive value (Area Under the Curve (AUC)) of each of the biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for control versus sepsis. In some embodiments, the methods or kits respectively described herein use any one of the biomarkers or genes listed in Table 24.

Table 24: Predictive value (AUC) of each of the biomarkers (single genes) of the biomarker panel for control versus sepsis, with HPRT1 as the housekeeping gene.

Up-regulated genes		Down-regulated genes	
Area Under the Curve		Area Under the Curve	
Genes	Area	Genes	Area
IL1RN	0.903	MAL	0.887
SLC22A4	0.820	CCR7	0.828
PLSCR1	0.916	GZMK	0.907
ANXA3	0.887	FCER1A	0.870
LRG1	0.877	FAIM3	0.882
C19ORF59	0.920	CD3D	0.923
ACSL1	0.901	CD6	0.830
PFKFB3	0.870	KLRB1	0.883
FFAR2	0.874	IL7R	0.836
FPR2	0.888	CCL5	0.864
HSPA1B	0.905		

NT5C3	0.865
DDX60L	0.888
SELL	0.902
IFITM1	0.902
RAB24	0.885
MCL1V1	0.862
PROK2	0.862
LILRA5	0.890
TLR4	0.871
NFIL3	0.903
IL1B	0.879
CYSTM1	0.906
CSF2RB	0.865
IFITM3	0.908
SOD2	0.860
FCGR1B	0.906
S100A12	0.908
SP100	0.896
NAIP	0.897

[00197] In some embodiments, the methods or kits respectively described herein use one or more, and in any combination, of the 40 biomarkers or genes listed in List 1.

[00198] Table 25 below shows the predictive value (Area Under Curve (AUC)) of exemplary sets of two biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Table 25 -- Continued

	HKG	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1	HPRT1
	Gene	NHL3	IL1B	CYSTM1	CSF2RB	IHTM3	SOD2	FCGR1B	S100A12	SP100	NAIP	MALI1	CCR7	GZMK	FCER1A	FAIM3	CD3D	CD6	KLRB1
HPRT1	IL1RN	0.81	0.80	0.81	0.80	0.81	0.80	0.81	0.82	0.80	0.81	0.81	0.79	0.82	0.80	0.81	0.82	0.80	0.82
HPRT1	SLC22A4	0.80	0.79	0.81	0.78	0.80	0.79	0.79	0.80	0.80	0.79	0.81	0.79	0.80	0.80	0.82	0.82	0.80	0.82
HPRT1	PUSCR1	0.82	0.81	0.82	0.81	0.81	0.81	0.81	0.83	0.81	0.82	0.81	0.80	0.83	0.81	0.82	0.83	0.81	0.82
HPRT1	ANXA3	0.81	0.80	0.81	0.79	0.81	0.80	0.80	0.81	0.80	0.81	0.81	0.80	0.81	0.80	0.82	0.83	0.81	0.82
HPRT1	LRG1	0.80	0.79	0.81	0.79	0.80	0.79	0.80	0.81	0.80	0.80	0.82	0.80	0.81	0.80	0.81	0.82	0.81	0.82
HPRT1	C19ORF59	0.82	0.81	0.83	0.81	0.82	0.81	0.82	0.83	0.82	0.82	0.83	0.81	0.82	0.81	0.82	0.83	0.82	0.83
HPRT1	ACS11	0.81	0.80	0.81	0.80	0.81	0.80	0.81	0.81	0.80	0.81	0.82	0.81	0.81	0.81	0.82	0.83	0.81	0.82
HPRT1	PFKB3	0.80	0.79	0.81	0.78	0.80	0.79	0.80	0.81	0.80	0.80	0.82	0.80	0.81	0.81	0.82	0.82	0.80	0.82
HPRT1	FFAR2	0.80	0.79	0.80	0.78	0.80	0.79	0.79	0.80	0.80	0.80	0.81	0.79	0.81	0.80	0.81	0.82	0.80	0.82
HPRT1	FPR2	0.81	0.80	0.81	0.79	0.81	0.80	0.80	0.81	0.80	0.80	0.82	0.80	0.81	0.80	0.82	0.82	0.81	0.82
HPRT1	HSPA1B	0.81	0.81	0.82	0.81	0.82	0.81	0.82	0.83	0.82	0.82	0.84	0.83	0.83	0.83	0.84	0.84	0.83	0.84
HPRT1	NT5C3	0.80	0.80	0.81	0.80	0.80	0.80	0.80	0.81	0.79	0.82	0.80	0.79	0.82	0.80	0.80	0.82	0.78	0.81
HPRT1	DDX60L	0.81	0.80	0.81	0.80	0.81	0.80	0.80	0.81	0.80	0.81	0.81	0.80	0.82	0.80	0.81	0.82	0.80	0.82
HPRT1	SELL	0.82	0.81	0.82	0.81	0.82	0.81	0.81	0.82	0.81	0.82	0.82	0.81	0.83	0.81	0.83	0.83	0.82	0.83
HPRT1	IFITM1	0.81	0.81	0.82	0.80	0.81	0.80	0.81	0.82	0.80	0.82	0.81	0.80	0.82	0.80	0.81	0.83	0.81	0.82
HPRT1	RAB24	0.81	0.80	0.82	0.80	0.81	0.80	0.81	0.81	0.81	0.81	0.82	0.80	0.82	0.81	0.82	0.82	0.81	0.82
HPRT1	MCL1	0.80	0.79	0.81	0.79	0.81	0.80	0.80	0.82	0.80	0.80	0.82	0.80	0.82	0.81	0.82	0.82	0.81	0.82
HPRT1	PROK2	0.80	0.79	0.81	0.79	0.81	0.80	0.80	0.81	0.80	0.80	0.81	0.80	0.81	0.80	0.81	0.82	0.80	0.82
HPRT1	LILRA5	0.81	0.81	0.82	0.80	0.81	0.80	0.80	0.81	0.81	0.81	0.81	0.80	0.81	0.80	0.81	0.82	0.81	0.82
HPRT1	TIR4	0.80	0.79	0.81	0.79	0.80	0.79	0.80	0.81	0.80	0.80	0.82	0.80	0.81	0.80	0.81	0.82	0.81	0.82

Table 25 – Continued

[illegible]

Table 25 – Continued

	HKG	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH
HKG	Gene	IL1RN	SIC22A4	PLSCR1	ANXA3	LRG1	C19ORF59	ACSL1	PKFB3	FFAR2	FPR2	HSPA1B	NTSC3	DX60L	SELL	IFITM1	RAB24	MCL1	PROK2	LILRA5	GAPDH	GAPDH	GAPDH
HPRT1	IL1RN	0.81	0.82	0.83	0.82	0.83	0.86	0.94	0.83	0.82	0.81	0.81	0.82	0.81	0.84	0.82	0.80	0.81	0.84	0.81	0.82	0.81	
HPRT1	SIC22A4	0.82	0.77	0.83	0.82	0.82	0.85	0.83	0.81	0.81	0.83	0.78	0.79	0.80	0.83	0.83	0.79	0.79	0.82	0.82	0.81	0.82	
HPRT1	PLSCR1	0.82	0.82	0.82	0.85	0.84	0.86	0.84	0.84	0.83	0.83	0.81	0.79	0.81	0.84	0.82	0.80	0.81	0.85	0.81	0.83	0.83	
HPRT1	ANXA3	0.82	0.80	0.82	0.82	0.83	0.85	0.83	0.82	0.81	0.82	0.80	0.81	0.81	0.84	0.83	0.80	0.81	0.83	0.82	0.82	0.82	
HPRT1	LRG1	0.82	0.79	0.83	0.83	0.83	0.85	0.83	0.81	0.81	0.82	0.80	0.81	0.81	0.84	0.83	0.80	0.80	0.83	0.82	0.81	0.81	
HPRT1	C19ORF59	0.83	0.82	0.84	0.84	0.84	0.86	0.85	0.83	0.83	0.83	0.82	0.82	0.83	0.85	0.85	0.81	0.82	0.84	0.83	0.84	0.84	
HPRT1	ACSL1	0.82	0.81	0.83	0.83	0.83	0.86	0.84	0.82	0.82	0.82	0.80	0.81	0.81	0.84	0.84	0.80	0.81	0.83	0.82	0.82	0.82	
HPRT1	PKFB3	0.82	0.79	0.83	0.83	0.82	0.85	0.83	0.81	0.81	0.82	0.79	0.80	0.81	0.84	0.83	0.79	0.80	0.82	0.81	0.82	0.82	
HPRT1	FFAR2	0.81	0.79	0.82	0.83	0.82	0.85	0.83	0.82	0.80	0.81	0.79	0.79	0.80	0.83	0.82	0.79	0.79	0.83	0.81	0.81	0.81	
HPRT1	FPR2	0.82	0.80	0.83	0.83	0.83	0.86	0.84	0.82	0.81	0.82	0.80	0.80	0.81	0.84	0.83	0.80	0.80	0.83	0.81	0.82	0.82	
HPRT1	HSPA1B	0.84	0.81	0.84	0.85	0.84	0.87	0.85	0.83	0.83	0.83	0.80	0.83	0.83	0.85	0.85	0.81	0.82	0.84	0.84	0.83	0.83	
HPRT1	NT5C3	0.80	0.80	0.80	0.83	0.83	0.86	0.83	0.82	0.81	0.81	0.80	0.75	0.79	0.82	0.80	0.78	0.79	0.84	0.81	0.81	0.81	
HPRT1	DDX60L	0.81	0.80	0.82	0.83	0.83	0.86	0.83	0.82	0.81	0.82	0.80	0.79	0.80	0.83	0.82	0.79	0.80	0.84	0.81	0.81	0.81	
HPRT1	SELL	0.82	0.81	0.83	0.84	0.84	0.86	0.84	0.83	0.82	0.82	0.81	0.81	0.82	0.84	0.84	0.81	0.81	0.84	0.82	0.83	0.83	
HPRT1	IFITM1	0.82	0.81	0.82	0.84	0.83	0.86	0.84	0.83	0.82	0.82	0.81	0.79	0.80	0.83	0.82	0.80	0.81	0.84	0.81	0.82	0.82	
HPRT1	RAB24	0.82	0.80	0.82	0.83	0.83	0.85	0.83	0.82	0.82	0.82	0.80	0.80	0.81	0.84	0.83	0.80	0.80	0.83	0.82	0.81	0.81	
HPRT1	MCL1	0.82	0.79	0.82	0.83	0.82	0.85	0.83	0.82	0.81	0.82	0.80	0.80	0.80	0.84	0.83	0.79	0.79	0.83	0.81	0.81	0.81	
HPRT1	PROK2	0.82	0.80	0.83	0.83	0.83	0.85	0.83	0.81	0.81	0.82	0.79	0.81	0.81	0.84	0.83	0.80	0.80	0.82	0.82	0.82	0.82	
HPRT1	LILRA5	0.82	0.81	0.82	0.83	0.84	0.85	0.84	0.82	0.82	0.82	0.80	0.80	0.81	0.84	0.83	0.80	0.81	0.84	0.81	0.82	0.82	
HPRT1	TIR4	0.81	0.79	0.83	0.83	0.83	0.85	0.84	0.81	0.81	0.82	0.79	0.80	0.81	0.84	0.83	0.79	0.80	0.83	0.82	0.81	0.81	

Table 25 – Continued

[illegible]

Table 25 – Continued

[illegible]

Table 25 -- Continued

[illegible]

Table 25 – Continued

[illegible]

Table 25 -- Continued

	HKG	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH	GAPDH
	Gene	IL1B	CYSTM1	CSF2RB	IFITM3	SOD2	FCGR1B	S100A12	SP100	NAIP	MAL1	CCR7	GZMK	FCER1A	FAIM3	CD3D	CD6	KLRB1	IL7R	GAPDH
HPRT1	HPRT1	0.83	0.82	0.85	0.81	0.82	0.81	0.85	0.79	0.83	0.84	0.85	0.84	0.84	0.84	0.84	0.84	0.84	0.85	0.85
HPRT1	SLC22A4	0.82	0.81	0.84	0.80	0.82	0.81	0.85	0.78	0.82	0.83	0.84	0.83	0.83	0.84	0.83	0.83	0.84	0.84	0.84
HPRT1	PLSCR1	0.84	0.83	0.85	0.83	0.82	0.82	0.86	0.80	0.84	0.84	0.85	0.85	0.84	0.85	0.85	0.84	0.85	0.85	0.85
HPRT1	ANXA3	0.84	0.82	0.84	0.81	0.83	0.81	0.84	0.80	0.83	0.84	0.84	0.84	0.83	0.84	0.84	0.84	0.84	0.84	0.84
HPRT1	LRG1	0.84	0.81	0.84	0.81	0.82	0.81	0.84	0.79	0.83	0.83	0.84	0.83	0.83	0.84	0.83	0.83	0.84	0.84	0.84
HPRT1	C19ORF59	0.85	0.83	0.85	0.83	0.84	0.83	0.85	0.81	0.84	0.84	0.85	0.84	0.84	0.85	0.85	0.84	0.85	0.85	0.85
HPRT1	ACSL1	0.84	0.82	0.84	0.81	0.83	0.82	0.85	0.80	0.83	0.84	0.85	0.84	0.84	0.84	0.84	0.84	0.84	0.85	0.85
HPRT1	PKF83	0.84	0.81	0.84	0.81	0.83	0.81	0.84	0.79	0.82	0.83	0.84	0.82	0.84	0.83	0.83	0.83	0.83	0.84	0.84
HPRT1	FFAR2	0.83	0.81	0.84	0.80	0.81	0.81	0.85	0.78	0.82	0.83	0.84	0.83	0.83	0.84	0.84	0.83	0.84	0.84	0.84
HPRT1	FPR2	0.84	0.82	0.84	0.81	0.82	0.81	0.85	0.79	0.83	0.84	0.85	0.83	0.83	0.84	0.84	0.84	0.84	0.85	0.84
HPRT1	HSPA1B	0.85	0.83	0.85	0.83	0.84	0.83	0.86	0.82	0.84	0.85	0.86	0.85	0.85	0.86	0.85	0.85	0.86	0.86	0.86
HPRT1	NT5C3	0.82	0.81	0.84	0.81	0.80	0.81	0.85	0.76	0.82	0.83	0.85	0.85	0.84	0.85	0.85	0.84	0.84	0.85	0.85
HPRT1	DDX60L	0.83	0.82	0.85	0.81	0.81	0.81	0.85	0.79	0.83	0.84	0.85	0.84	0.84	0.85	0.85	0.84	0.85	0.85	0.85
HPRT1	SELL	0.84	0.83	0.85	0.82	0.83	0.82	0.85	0.81	0.84	0.84	0.85	0.85	0.84	0.85	0.85	0.85	0.85	0.85	0.85
HPRT1	IFITM1	0.83	0.82	0.85	0.81	0.81	0.82	0.85	0.79	0.83	0.84	0.85	0.84	0.84	0.85	0.85	0.84	0.84	0.85	0.85
HPRT1	RAB24	0.83	0.82	0.84	0.81	0.82	0.81	0.85	0.79	0.83	0.84	0.85	0.84	0.84	0.85	0.85	0.84	0.84	0.85	0.85
HPRT1	MCL1	0.83	0.81	0.84	0.81	0.82	0.81	0.85	0.79	0.83	0.84	0.85	0.84	0.84	0.84	0.84	0.84	0.84	0.85	0.84
HPRT1	PROK2	0.83	0.82	0.84	0.81	0.82	0.81	0.85	0.79	0.82	0.84	0.84	0.83	0.84	0.84	0.84	0.84	0.84	0.84	0.84
HPRT1	LILRA5	0.84	0.82	0.85	0.82	0.81	0.82	0.85	0.79	0.83	0.84	0.85	0.84	0.84	0.84	0.84	0.84	0.84	0.85	0.84
HPRT1	TLR4	0.83	0.81	0.84	0.81	0.82	0.81	0.85	0.79	0.82	0.83	0.84	0.83	0.84	0.84	0.83	0.83	0.83	0.84	0.84

Table 25 - Continued

[illegible]

[00199] Table 26 below shows the weights given to each of the biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for control/infection without SIRS/SIRS without infection versus mild sepsis/severe sepsis/septic shock.

Table 26: Weights were given to each of the biomarkers or genes of the biomarker panel to allow the scoring algorithm for segregating control/infection without SIRS/SIRS without infection versus mild sepsis/severe sepsis/septic shock (Figure 4), with HPRT1/GAPDH as the housekeeping gene (n=151, where “n” is the number of samples).

No.	HKG	Gene	Weight
1	HPRT1	IL1RN	-0.09
2	HPRT1	SLC22A4	-0.12
3	HPRT1	PLSCR1	-0.13
4	HPRT1	ANXA3	-0.08
5	HPRT1	LRG1	-0.07
6	HPRT1	C19ORF59	-0.09
7	HPRT1	ACSL1	-0.09
8	HPRT1	PFKFB3	-0.10
9	HPRT1	FFAR2	-0.08
10	HPRT1	FPR2	-0.11
11	HPRT1	HSPA1B	-0.15
12	HPRT1	NT5C3	-0.14
13	HPRT1	DDX60L	-0.13
14	HPRT1	SELL	-0.16
15	HPRT1	IFITM1	-0.13
16	HPRT1	RAB24	-0.16
17	HPRT1	MCL1	-0.17
18	HPRT1	PROK2	-0.08
19	HPRT1	LILRA5	-0.12
20	HPRT1	TLR4	-0.12
21	HPRT1	NFIL3	-0.13
22	HPRT1	IL1B	-0.09
23	HPRT1	CYSTM1	-0.10
24	HPRT1	CSF2RB	-0.11
25	HPRT1	IFITM3	-0.13

26	HPRT1	SOD2	-0.10
27	HPRT1	FCGR1B	-0.10
28	HPRT1	S100A12	-0.10
29	HPRT1	SP100	-0.16
30	HPRT1	NAIP	-0.12
31	HPRT1	MAL1	0.13
32	HPRT1	CCR7	0.15
33	HPRT1	GZMK	0.15
34	HPRT1	FCER1A	0.11
35	HPRT1	FAIM3	0.18
36	HPRT1	CD3D	0.18
37	HPRT1	CD6	0.16
38	HPRT1	KLRB1	0.16
39	HPRT1	IL7R	0.15
40	HPRT1	CCL5	0.17
41	GAPDH	IL1RN	-0.13
42	GAPDH	SLC22A4	-0.16
43	GAPDH	PLSCR1	-0.16
44	GAPDH	ANXA3	-0.12
45	GAPDH	LRG1	-0.11
46	GAPDH	C19ORF59	-0.14
47	GAPDH	ACSL1	-0.13
48	GAPDH	PFKFB3	-0.16
49	GAPDH	FFAR2	-0.12
50	GAPDH	FPR2	-0.17
51	GAPDH	HSPA1B	-0.13
52	GAPDH	NT5C3	-0.09
53	GAPDH	DDX60L	-0.17
54	GAPDH	SELL	-0.26
55	GAPDH	IFITM1	-0.19
56	GAPDH	RAB24	-0.20
57	GAPDH	MCL1	-0.26
58	GAPDH	PROK2	-0.12
59	GAPDH	LILRA5	-0.18
60	GAPDH	TLR4	-0.20
61	GAPDH	NFIL3	-0.20
62	GAPDH	IL1B	-0.14
63	GAPDH	CYSTM1	-0.15
64	GAPDH	CSF2RB	-0.16
65	GAPDH	IFITM3	-0.19
66	GAPDH	SOD2	-0.14

67	GAPDH	FCGR1B	-0.13
68	GAPDH	S100A12	-0.16
69	GAPDH	SP100	-0.12
70	GAPDH	NAIP	-0.20
71	GAPDH	MAL1	0.12
72	GAPDH	CCR7	0.17
73	GAPDH	GZMK	0.12
74	GAPDH	FCER1A	0.11
75	GAPDH	FAIM3	0.15
76	GAPDH	CD3D	0.14
77	GAPDH	CD6	0.15
78	GAPDH	KLRB1	0.12
79	GAPDH	IL7R	0.15
80	GAPDH	CCL5	0.14

[00200] Table 27 below shows the weights given to each of the biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for mild sepsis versus severe sepsis/septic shock.

Table 27: Weights were given to each of the biomarkers or genes of the biomarker panel for mild sepsis versus severe sepsis/septic shock, (Figure 5), with HPRT1/GAPDH as the housekeeping gene (n=85, where “n” is the number of samples).

No.	HKG	Gene	Weight
1	HPRT1	IL1RN	-0.06
2	HPRT1	SLC22A4	0.00
3	HPRT1	PLSCR1	-0.09
4	HPRT1	ANXA3	-0.06
5	HPRT1	LRG1	-0.05
6	HPRT1	C19ORF59	-0.07
7	HPRT1	ACSL1	-0.06
8	HPRT1	PFKFB3	-0.06
9	HPRT1	FFAR2	-0.05
10	HPRT1	FPR2	-0.07
11	HPRT1	HSPA1B	-0.06
12	HPRT1	NT5C3	0.00
13	HPRT1	DDX60L	-0.03
14	HPRT1	SELL	-0.06
15	HPRT1	IFITM1	-0.08

16	HPRT1	RAB24	-0.09
17	HPRT1	MCL1	0.00
18	HPRT1	PROK2	-0.03
19	HPRT1	LILRA5	-0.05
20	HPRT1	TLR4	-0.07
21	HPRT1	NFIL3	-0.08
22	HPRT1	IL1B	-0.05
23	HPRT1	CYSTM1	-0.06
24	HPRT1	CSF2RB	-0.05
25	HPRT1	IFITM3	-0.07
26	HPRT1	SOD2	-0.07
27	HPRT1	FCGR1B	-0.08
28	HPRT1	S100A12	-0.07
29	HPRT1	SP100	-0.07
30	HPRT1	NAIP	-0.05
31	HPRT1	MAL1	0.06
32	HPRT1	CCR7	0.10
33	HPRT1	GZMK	0.10
34	HPRT1	FCER1A	0.09
35	HPRT1	FAIM3	0.12
36	HPRT1	CD3D	0.12
37	HPRT1	CD6	0.09
38	HPRT1	KLRB1	0.09
39	HPRT1	IL7R	0.08
40	HPRT1	CCL5	0.07
41	GAPDH	IL1RN	-0.05
42	GAPDH	SLC22A4	0.00
43	GAPDH	PLSCR1	0.00
44	GAPDH	ANXA3	-0.06
45	GAPDH	LRG1	-0.06
46	GAPDH	C19ORF59	-0.08
47	GAPDH	ACSL1	-0.08
48	GAPDH	PFKFB3	-0.05
49	GAPDH	FFAR2	0.00
50	GAPDH	FPR2	-0.09
51	GAPDH	HSPA1B	-0.05
52	GAPDH	NT5C3	0.00
53	GAPDH	DDX60L	0.00
54	GAPDH	SELL	0.00
55	GAPDH	IFITM1	-0.04
56	GAPDH	RAB24	-0.07
57	GAPDH	MCL1	0.00
58	GAPDH	PROK2	-0.03
59	GAPDH	LILRA5	0.00

60	GAPDH	TLR4	-0.08
61	GAPDH	NFIL3	-0.07
62	GAPDH	IL1B	0.00
63	GAPDH	CYSTM1	-0.07
64	GAPDH	CSF2RB	-0.06
65	GAPDH	IFITM3	0.00
66	GAPDH	SOD2	-0.08
67	GAPDH	FCGR1B	-0.08
68	GAPDH	S100A12	-0.08
69	GAPDH	SP100	0.00
70	GAPDH	NAIP	0.00
71	GAPDH	MAL1	0.07
72	GAPDH	CCR7	0.10
73	GAPDH	GZMK	0.08
74	GAPDH	FCER1A	0.08
75	GAPDH	FAIM3	0.10
76	GAPDH	CD3D	0.08
77	GAPDH	CD6	0.09
78	GAPDH	KLRB1	0.08
79	GAPDH	IL7R	0.09
80	GAPDH	CCL5	0.07

[00201] In some embodiments, the methods or kits respectively described herein use any five of the 40 biomarkers or genes listed in List 1.

[00202] Table 28 below shows the predictive value (Area Under Curve (AUC)) of exemplary sets of five biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Table 28: Predictive value (AUC) of exemplary sets of five biomarkers or genes of the biomarker panel for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Gene1	Gene2	Gene3	Gene4	Gene5	Specificity	Sensitivity	AUC
IFITM3	SELL	MCL1	FPR2	CD3D	0.73	0.87	0.84
FPR2	NT5C3	CCL5	HSPA1B	SLC22A4	0.72	0.94	0.84
S100A12	HSPA1B	CCL5	ACSL1	CD6	0.74	0.90	0.84
FAIM3	CYSTM1	KLRB1	SLC22A4	MAL1	0.74	0.89	0.84
CSF2RB	KLRB1	IL1RN	SP100	CYSTM1	0.70	0.91	0.84
FFAR2	HSPA1B	CCL5	IL7R	CYSTM1	0.75	0.87	0.84

IL7R	CYSTM1	S100A12	C19ORF59	ANXA3	0.74	0.86	0.84
RAB24	DDX60L	CYSTM1	KLRB1	PFKFB3	0.72	0.90	0.84
SELL	CYSTM1	HSPA1B	MCL1	CCL5	0.78	0.84	0.85
ACSL1	CD6	GZMK	HSPA1B	PFKFB3	0.72	0.91	0.84
MAL1	RAB24	HSPA1B	IL7R	CCL5	0.73	0.90	0.85
NAIP	HSPA1B	CYSTM1	IL7R	CCL5	0.74	0.89	0.84
PROK2	KLRB1	HSPA1B	NAIP	FPR2	0.74	0.86	0.84
IFITM1	KLRB1	GZMK	TLR4	HSPA1B	0.72	0.89	0.85
NT5C3	HSPA1B	PROK2	C19ORF59	FFAR2	0.72	0.93	0.84
PFKFB3	SLC22A4	LILRA5	HSPA1B	KLRB1	0.78	0.80	0.85
TLR4	ACSL1	DDX60L	FAIM3	HSPA1B	0.72	0.90	0.84
FCER1A	CCL5	HSPA1B	CYSTM1	C19ORF59	0.73	0.91	0.85
KLRB1	CCL5	HSPA1B	NT5C3	FCGR1B	0.74	0.90	0.84
C19ORF59	FPR2	CD6	HSPA1B	PFKFB3	0.73	0.90	0.85
CYSTM1	MAL1	HSPA1B	CCL5	IL7R	0.73	0.89	0.85
DDX60L	CSF2RB	HSPA1B	CCL5	FFAR2	0.73	0.94	0.84
GZMK	TLR4	HSPA1B	C19ORF59	IL1RN	0.72	0.94	0.84
ANXA3	IL7R	CCR7	KLRB1	HSPA1B	0.75	0.83	0.84
CCR7	FPR2	KLRB1	CYSTM1	MCL1	0.73	0.89	0.84
IL1RN	IL7R	CCR7	KLRB1	CYSTM1	0.72	0.90	0.84
LILRA5	TLR4	KLRB1	HSPA1B	CD6	0.78	0.83	0.85
CD3D	HSPA1B	IL1RN	RAB24	SELL	0.75	0.89	0.84
CD6	PFKFB3	LILRA5	CCL5	HSPA1B	0.73	0.93	0.85
HSPA1B	PFKFB3	CD6	DDX60L	CCL5	0.72	0.93	0.85
IL1B	CCL5	HSPA1B	FCGR1B	TLR4	0.72	0.93	0.85
MCL1	CYSTM1	KLRB1	C19ORF59	HSPA1B	0.74	0.86	0.84
LRG1	IL1RN	C19ORF59	HSPA1B	NFIL3	0.73	0.90	0.84
PLSCR1	SOD2	HSPA1B	IL7R	CCL5	0.72	0.94	0.85
CCL5	HSPA1B	CD6	ANXA3	FAIM3	0.70	0.90	0.85
FCGR1B	KLRB1	PLSCR1	CYSTM1	CCR7	0.73	0.87	0.84
NFIL3	S100A12	HSPA1B	LILRA5	IFITM3	0.77	0.84	0.84
SOD2	HSPA1B	CSF2RB	KLRB1	FCGR1B	0.75	0.83	0.84
SLC22A4	HSPA1B	GZMK	CYSTM1	FCGR1B	0.73	0.90	0.84
SP100	HSPA1B	CCR7	GZMK	CD3D	0.73	0.87	0.84

[00203] In some embodiments, the methods or kits respectively described herein use any ten of the 40 biomarkers or genes listed in List 1.

[00204] Table 29 below shows the predictive value (Area Under Curve (AUC)) of exemplary sets of ten biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Table 29: Predictive value (AUC) of exemplary sets of ten biomarkers or genes of the biomarker panel for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Gene1	Gene2	Gene3	Gene4	Gene5	Gene6	Gene7	Gene8	Gene9	Gene10	Specificity	Sensitivity	AUC
ACSL1	HSPA1B	SOD2	ANXA3	IFITM3	FPR2	RAB24	CYSTM1	C19ORF59	CD3D	0.72	0.97	0.85
ANXA3	HSPA1B	SLC22A4	NT5C3	C19ORF59	PROK2	CYSTM1	NFIL3	TLR4	FCGR1B	0.73	0.93	0.86
C19ORF59	PFKFB3	NT5C3	IL7R	HSPA1B	FFAR2	GZMK	IFITM3	ACSL1	FPR2	0.70	0.94	0.86
CCL5	SLC22A4	CD6	IL7R	NFIL3	FCGR1B	HSPA1B	TLR4	IL1B	IL1RN	0.70	0.94	0.86
CCR7	FPR2	MCL1	TLR4	IFITM1	ANXA3	PLSCR1	MAL1	HSPA1B	CSF2RB	0.73	0.89	0.85
CD3D	LILRA5	C19ORF59	FCER1A	SELL	MCL1	HSPA1B	DDX60L	PFKFB3	CYSTM1	0.69	0.94	0.86
CD6	C19ORF59	TLR4	FCGR1B	MAL1	KLRB1	HSPA1B	SLC22A4	CCL5	PLSCR1	0.63	0.99	0.86
CSF2RB	C19ORF59	KLRB1	IFITM1	SP100	TLR4	CCL5	IFITM3	HSPA1B	NFIL3	0.77	0.89	0.87
CYSTM1	FCGR1B	MAL1	PROK2	TLR4	FPR2	IL1RN	CD3D	HSPA1B	ACSL1	0.67	0.99	0.85
DDX60L	S100A12	CCR7	TLR4	SP100	CSF2RB	HSPA1B	RAB24	LRG1	SOD2	0.73	0.90	0.85
FAIM3	IFITM1	MCL1	HSPA1B	LRG1	CYSTM1	TLR4	CCR7	CSF2RB	FPR2	0.70	0.93	0.85
FCER1A	LILRA5	CYSTM1	NFIL3	HSPA1B	C19ORF59	NAIP	LRG1	SELL	CSF2RB	0.73	0.91	0.85
FCGR1B	MCL1	NAIP	LRG1	GZMK	DDX60L	PFKFB3	HSPA1B	PROK2	IFITM3	0.70	0.90	0.85
FFAR2	FCER1A	IL1B	TLR4	ANXA3	CCL5	ACSL1	IL1RN	SLC22A4	HSPA1B	0.77	0.91	0.86
FPR2	NAIP	FFAR2	SELL	IFITM1	PLSCR1	CD3D	PFKFB3	TLR4	CYSTM1	0.70	0.94	0.85
GZMK	C19ORF59	LRG1	DDX60L	LILRA5	FCGR1B	TLR4	HSPA1B	S100A12	SP100	0.72	0.93	0.86
HSPA1B	KLRB1	TLR4	RAB24	CCL5	NAIP	MAL1	IL7R	FCER1A	IFITM3	0.73	0.96	0.87
IFITM1	CD6	SELL	CCR7	FCGR1B	SP100	PROK2	HSPA1B	TLR4	IFITM3	0.70	0.96	0.87
IFITM3	FCGR1B	PROK2	HSPA1B	CCL5	IL7R	C19ORF59	TLR4	FFAR2	IL1B	0.72	0.94	0.86
IL1B	IL1RN	C19ORF59	ANXA3	LILRA5	HSPA1B	CYSTM1	KLRB1	S100A12	TLR4	0.77	0.89	0.86
IL1RN	CSF2RB	SOD2	HSPA1B	IFITM1	SELL	MCL1	FFAR2	CCL5	PROK2	0.74	0.90	0.85
IL7R	CSF2RB	HSPA1B	TLR4	CD3D	CCL5	FFAR2	RAB24	CYSTM1	MAL1	0.73	0.93	0.86
KLRB1	FPR2	CCR7	CYSTM1	RAB24	CCL5	SP100	LILRA5	S100A12	SELL	0.74	0.89	0.85

LILRA5	LRG1	MCL1	DDX60L	CD3D	IL1RN	SELL	HSPA1B	ANXA3	IL1B	0.74	0.90	0.85
LRG1	TLR4	CD3D	SLC22A4	MAL1	ANXA3	IFITM3	HSPA1B	SP100	S100A12	0.75	0.91	0.86
MAL1	CYSTM1	SELL	IFITM1	TLR4	SOD2	CCR7	FPR2	HSPA1B	CCL5	0.72	0.94	0.85
NAIP	NFIL3	CCR7	IFITM1	KLRB1	TLR4	LRG1	PLSCR1	FCER1A	FPR2	0.64	0.97	0.85
NFIL3	CSF2RB	SOD2	TLR4	SLC22A4	ANXA3	C19ORF59	IL1B	IL7R	HSPA1B	0.69	0.93	0.86
MCL1	ANXA3	LRG1	SP100	S100A12	CD3D	SELL	FCGR1B	PROK2	PLSCR1	0.74	0.91	0.84
NT5C3	MCL1	LRG1	S100A12	HSPA1B	DDX60L	IL1RN	IL1B	C19ORF59	LILRA5	0.77	0.86	0.85
PFKFB3	TLR4	ACSL1	PROK2	CCR7	ANXA3	RAB24	CYSTM1	HSPA1B	GZMK	0.72	0.90	0.86
PLSCR1	S100A12	TLR4	SP100	IL7R	MAL1	GZMK	IFITM1	KLRB1	ACSL1	0.73	0.90	0.84
PROK2	FCGR1B	NFIL3	HSPA1B	CCL5	IFITM3	TLR4	FPR2	C19ORF59	SELL	0.74	0.91	0.86
RAB24	SELL	HSPA1B	CCR7	IL1B	TLR4	NAIP	IL1RN	ACSL1	CYSTM1	0.74	0.96	0.86
S100A12	CCL5	IL1B	LILRA5	NAIP	CYSTM1	SELL	IL1RN	TLR4	IFITM1	0.74	0.90	0.85
SELL	KLRB1	MCL1	CD6	LRG1	CCR7	GZMK	HSPA1B	NT5C3	IFITM3	0.74	0.87	0.85
SLC22A4	HSPA1B	IL7R	CYSTM1	CCL5	ACSL1	FAIM3	LRG1	PLSCR1	RAB24	0.74	0.91	0.86
SOD2	CCR7	C19ORF59	IFITM1	RAB24	NAIP	CYSTM1	SELL	PFKFB3	SLC22A4	0.74	0.91	0.85
SP100	FPR2	NAIP	LILRA5	CD6	FFAR2	IFITM3	CSF2RB	TLR4	HSPA1B	0.75	0.90	0.87
TLR4	C19ORF59	IL1B	FAIM3	IFITM3	HSPA1B	GZMK	ACSL1	CCR7	SP100	0.75	0.91	0.86

[00205] In some embodiments, the methods or kits respectively described herein use any twenty of the 40 biomarkers or genes listed in List 1.

[00206] Table 30 below shows the predictive value (Area Under Curve (AUC)) of exemplary sets of twenty biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Table 30: Predictive value (AUC) of exemplary sets of twenty biomarkers or genes of the biomarker panel for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Gene1	ACSL1	ANXA3	C19ORF59	CCL5	CCR7	CD3D	CD6	CSF2RB	CYSTM1	DDX60L
Gene2	IFITM1	C19ORF59	PFKFB3	FCER1A	HSPA1B	SELL	PLSCR1	PROK2	SOD2	PROK2
Gene3	CSF2RB	MCL1	MAL1	ANXA3	FCGR1B	NFIL3	IFITM1	FFAR2	KLRB1	NAIP
Gene4	HSPA1B	PFKFB3	IFITM3	SP100	SLC22A4	GZMK	IL7R	MCL1	SP100	HSPA1B
Gene5	PFKFB3	TLR4	HSPA1B	HSPA1B	TLR4	IL7R	KLRB1	CD3D	HSPA1B	FCGR1B
Gene6	FPR2	CCL5	KLRB1	NAIP	PFKFB3	HSPA1B	C19ORF59	CCL5	IL7R	IFITM3
Gene7	RAB24	DDX60L	SP100	PROK2	NFIL3	IFITM1	ANXA3	IFITM1	ANXA3	SLC22A4
Gene8	ANXA3	NT5C3	TLR4	CD6	CD3D	PROK2	SOD2	ANXA3	FAIM3	MAL1
Gene9	PLSCR1	NAIP	IFITM1	DDX60L	GZMK	NAIP	TLR4	TLR4	RAB24	S100A12
Gene10	FCER1A	LILRA5	CCR7	PFKFB3	IL1RN	ACSL1	NT5C3	CYSTM1	TLR4	NT5C3
Gene11	CD3D	IFITM3	LRG1	SOD2	FCER1A	IFITM3	IFITM3	PLSCR1	NT5C3	TLR4
Gene12	FFAR2	IL1RN	FCGR1B	TLR4	SOD2	CCL5	SLC22A4	IFITM3	IFITM1	CCL5
Gene13	NAIP	FAIM3	CD6	IL7R	SP100	C19ORF59	SP100	FCER1A	PLSCR1	IFITM1
Gene14	KLRB1	CCR7	RAB24	KLRB1	KLRB1	ANXA3	NAIP	SP100	CCL5	SELL
Gene15	MAL1	LRG1	MCL1	CD3D	ACSL1	PFKFB3	CYSTM1	PFKFB3	FPR2	IL1B
Gene16	TLR4	NFIL3	CYSTM1	CCR7	IFITM3	TLR4	FAIM3	IL1B	FCGR1B	FPR2
Gene17	CYSTM1	HSPA1B	NAIP	IFITM1	LRG1	FCGR1B	CCL5	CD6	NAIP	PFKFB3
Gene18	CD6	SP100	NT5C3	CYSTM1	IL1B	SP100	DDX60L	C19ORF59	LRG1	C19ORF59
Gene19	CCL5	SLC22A4	CCL5	S100A12	MCL1	PLSCR1	IL1RN	HSPA1B	SELL	CCR7
Gene20	IFITM3	IFITM1	IL1RN	IFITM3	C19ORF59	RAB24	HSPA1B	GZMK	IFITM3	FAIM3
Specificity	0.74	0.75	0.75	0.78	0.80	0.75	0.80	0.75	0.77	0.75
Sensitivity	0.93	0.90	0.94	0.91	0.86	0.94	0.89	0.94	0.93	0.90
AUC	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89

Table 30 – Continued

Gene1	FAIM3	FCER1A	FCGR1B	FFAR2	FPR2	GZMK	HSPA1B	IFITM1	IFITM3	IL1B
Gene2	C19ORF59	PROK2	SLC22A4	LRG1	KLRB1	CCL5	MAL1	FFAR2	ACSL1	PFKFB3
Gene3	HSPA1B	SOD2	IFITM3	MAL1	RAB24	TLR4	NFIL3	TLR4	RAB24	ANXA3
Gene4	CSF2RB	PFKFB3	TLR4	IL1RN	C19ORF59	CD3D	CCL5	PLSCR1	SOD2	KLRB1
Gene5	IL7R	MCL1	FAIM3	IFITM3	CYSTM1	S100A12	GZMK	C19ORF59	TLR4	IFITM1
Gene6	LILRA5	SP100	PLSCR1	C19ORF59	CD6	CCR7	LRG1	CCL5	NAIP	TLR4
Gene7	MCL1	IFITM3	NT5C3	NFIL3	NAIP	IL1RN	SLC22A4	SLC22A4	S100A12	FFAR2
Gene8	IFITM1	KLRB1	KLRB1	HSPA1B	FCER1A	C19ORF59	KLRB1	LILRA5	PLSCR1	HSPA1B
Gene9	SP100	DDX60L	C19ORF59	IL1B	IFITM3	RAB24	S100A12	FAIM3	IL1RN	PLSCR1
Gene10	PROK2	TLR4	FFAR2	PROK2	FAIM3	IL7R	PFKFB3	LRG1	FPR2	SP100
Gene11	IFITM3	IL7R	IL1B	DDX60L	MCL1	MCL1	CYSTM1	DDX60L	SP100	CCR7
Gene12	SLC22A4	C19ORF59	HSPA1B	TLR4	PROK2	NAIP	DDX60L	HSPA1B	CCR7	RAB24
Gene13	PLSCR1	LRG1	SP100	IFITM1	CD3D	NT5C3	IFITM1	SP100	NFIL3	CD3D
Gene14	CD3D	IFITM1	SOD2	SP100	PROK2	LILRA5	FFAR2	IFITM3	CD3D	MAL1
Gene15	SELL	HSPA1B	CSF2RB	CCL5	ANXA3	IFITM1	C19ORF59	PFKFB3	CCL5	IFITM3
Gene16	CCL5	RAB24	MCL1	NAIP	HSPA1B	HSPA1B	TLR4	ANXA3	SELL	SOD2
Gene17	NAIP	PLSCR1	SELL	ACSL1	TLR4	LRG1	PROK2	MAL1	PROK2	FCER1A
Gene18	TLR4	CCR7	ANXA3	SOD2	CCR7	PFKFB3	NAIP	IL7R	LRG1	ACSL1
Gene19	KLRB1	CD6	RAB24	MCL1	IFITM1	SP100	IFITM3	CD6	HSPA1B	LRG1
Gene20	FCGR1B	LILRA5	IFITM1	LILRA5	CCL5	IFITM3	SP100	ACSL1	IFITM1	C19ORF59
Specificity	0.80	0.74	0.74	0.80	0.78	0.78	0.79	0.78	0.79	0.74
Sensitivity	0.87	0.97	0.96	0.87	0.90	0.93	0.90	0.90	0.94	0.94
AUC	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89

Table 30 – Continued

Gene1	IL1RN	IL7R	KLRB1	LILRA5	LRG1	MAL1	MCL1	NAIP	NFIL3	NT5C3
Gene2	HSPA1B	FCGR1B	MAL1	SLC22A4	IL1B	S100A12	C19ORF59	IL1B	SELL	HSPA1B
Gene3	NT5C3	CCL5	CCL5	SP100	S100A12	NFIL3	RAB24	NFIL3	FCER1A	LRG1
Gene4	LRG1	FAIM3	HSPA1B	CCL5	HSPA1B	FPR2	ANXA3	TLR4	GZMK	NAIP
Gene5	ACSL1	LRG1	NFIL3	MAL1	NAIP	SLC22A4	CSF2RB	FCER1A	MAL1	SLC22A4
Gene6	CYSTM1	RAB24	RAB24	IFITM3	PLSCR1	TLR4	CCL5	FPR2	CCL5	LILRA5
Gene7	IFITM3	PROK2	IFITM1	PROK2	PROK2	NAIP	IFITM1	SLC22A4	NAIP	TLR4
Gene8	FAIM3	NAIP	IL1B	TLR4	CCL5	CCR7	SLC22A4	SELL	C19ORF59	SOD2
Gene9	MCL1	LILRA5	SELL	SELL	IL7R	HSPA1B	IFITM3	KLRB1	ACSL1	PFKFB3
Gene10	CD6	HSPA1B	LILRA5	DDX60L	C19ORF59	KLRB1	DDX60L	SP100	TLR4	ACSL1
Gene11	RAB24	CD6	IFITM3	FPR2	GZMK	IFITM3	SOD2	LRG1	NT5C3	IL1B
Gene12	CCR7	IL1RN	NAIP	ACSL1	SELL	CYSTM1	CYSTM1	IL7R	HSPA1B	CSF2RB
Gene13	SP100	SP100	S100A12	HSPA1B	SP100	IL1RN	PFKFB3	PFKFB3	SP100	FFAR2
Gene14	IFITM1	TLR4	TLR4	FAIM3	FCGR1B	PFKFB3	S100A12	IFITM3	IFITM3	C19ORF59
Gene15	NAIP	CSF2RB	ACSL1	LRG1	TLR4	IL1B	TLR4	CD6	PFKFB3	SP100
Gene16	SELL	IFITM1	NT5C3	GZMK	RAB24	PLSCR1	CCR7	LILRA5	IFITM1	IFITM3
Gene17	CCL5	SELL	LRG1	PFKFB3	SOD2	IFITM1	NAIP	IL1RN	CD6	FAIM3
Gene18	TLR4	FFAR2	PROK2	IL1RN	IFITM3	ACSL1	KLRB1	HSPA1B	RAB24	GZMK
Gene19	PLSCR1	IFITM3	SP100	IL7R	FPR2	ANXA3	CD6	CYSTM1	LILRA5	KLRB1
Gene20	NFIL3	SOD2	IL7R	KLRB1	MAL1	C19ORF59	HSPA1B	ACSL1	IL1RN	ANXA3
Specificity	0.78	0.74	0.79	0.75	0.77	0.79	0.77	0.77	0.75	0.79
Sensitivity	0.94	0.94	0.94	0.90	0.90	0.87	0.90	0.90	0.96	0.89
AUC	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89

Table 30 – Continued

Gene1	PFKFB3	PLSCR1	PROK2	RAB24	S100A12	SELL	SLC22A4	SOD2	SP100	TLR4
Gene2	DDX60L	FAIM3	MCL1	SLC22A4	GZMK	NFIL3	KLRB1	RAB24	ACSL1	CCL5
Gene3	CSF2RB	C19ORF59	HSPA1B	NAIP	SOD2	IFITM1	LRG1	IL1B	IFITM3	IFITM1
Gene4	LRG1	ACSL1	C19ORF59	IL7R	MAL1	IFITM3	MCL1	IL1RN	CCL5	C19ORF59
Gene5	KLRB1	GZMK	S100A12	FFAR2	TLR4	CYSTM1	GZMK	IFITM1	HSPA1B	IL7R
Gene6	CCL5	IL7R	IFITM3	KLRB1	KLRB1	DDX60L	PFKFB3	SP100	MAL1	HSPA1B
Gene7	NAIP	TLR4	PFKFB3	SOD2	SLC22A4	FCER1A	HSPA1B	LILRA5	TLR4	PROK2
Gene8	PROK2	PFKFB3	TLR4	CYSTM1	HSPA1B	IL1RN	IFITM1	MCL1	RAB24	ANXA3
Gene9	SELL	HSPA1B	IL1B	LRG1	SP100	CCR7	IFITM3	IFITM3	LRG1	MCL1
Gene10	NFIL3	S100A12	CD6	IFITM1	PLSCR1	NAIP	C19ORF59	TLR4	CYSTM1	RAB24
Gene11	CCR7	FFAR2	IL1RN	C19ORF59	CCL5	PFKFB3	MAL1	CD3D	IFITM1	SOD2
Gene12	SP100	NT5C3	CCL5	CSF2RB	PFKFB3	CD3D	LILRA5	FPR2	GZMK	PLSCR1
Gene13	IFITM1	SP100	SP100	NT5C3	FFAR2	SP100	ACSL1	GZMK	KLRB1	FCER1A
Gene14	IFITM3	PROK2	LRG1	SP100	C19ORF59	C19ORF59	S100A12	ANXA3	C19ORF59	CSF2RB
Gene15	TLR4	IFITM3	LILRA5	ANXA3	IFITM1	CCL5	SP100	C19ORF59	PFKFB3	GZMK
Gene16	GZMK	ANXA3	SOD2	IL1B	FCER1A	TLR4	TLR4	PFKFB3	LILRA5	DDX60L
Gene17	FPR2	SLC22A4	DDX60L	LILRA5	CYSTM1	NT5C3	PROK2	IL7R	CD6	MAL1
Gene18	C19ORF59	SOD2	IFITM1	HSPA1B	LRG1	FCGR1B	IL1RN	CYSTM1	SELL	LRG1
Gene19	HSPA1B	MCL1	IL7R	IFITM3	IFITM3	S100A12	NT5C3	CCL5	FAIM3	SP100
Gene20	IL7R	IFITM1	RAB24	TLR4	DDX60L	HSPA1B	FFAR2	HSPA1B	PROK2	IFITM3
Specificity	0.74	0.77	0.77	0.75	0.74	0.78	0.77	0.74	0.75	0.77
Sensitivity	0.94	0.96	0.91	0.94	0.94	0.89	0.93	0.94	0.96	0.97
AUC	0.89	0.89	0.90	0.89	0.89	0.89	0.89	0.89	0.89	0.89

[00207] In some embodiments, the methods or kits respectively described herein use any thirty of the 40 biomarkers or genes listed in List 1.

[00208] Table 31 below shows the predictive value (Area Under Curve (AUC)) of exemplary sets of thirty biomarkers of the biomarker panel of the 40 biomarkers or genes listed in List 1 for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Table 31: Predictive value (AUC) of exemplary sets of thirty biomarkers or genes of the biomarker panel for control versus sepsis, with HPRT1/GAPDH as the housekeeping gene.

Gene1	ACSL1	ANXA3	C19ORF59	CCL5	CCR7	CD3D	CD6	CSF2RB
Gene2	KLRB1	LRG1	NAIP	TLR4	CD3D	ANXA3	SOD2	C19ORF59
Gene3	PFKFB3	SLC22A4	S100A12	CYSTM1	SP100	TLR4	IL1B	CD3D
Gene4	SLC22A4	ACSL1	TLR4	LILRA5	LRG1	C19ORF59	C19ORF59	FFAR2
Gene5	LRG1	NFIL3	PFKFB3	C19ORF59	LILRA5	MAL1	CYSTM1	IFITM1
Gene6	IL1B	CD6	LRG1	PFKFB3	RAB24	RAB24	KLRB1	DDX60L
Gene7	C19ORF59	PROK2	IL1B	MAL1	ACSL1	FFAR2	MAL1	SP100
Gene8	RAB24	CCL5	SOD2	FCER1A	S100A12	KLRB1	SELL	TLR4
Gene9	CYSTM1	SP100	LILRA5	HSPA1B	FFAR2	IFITM3	GZMK	CYSTM1
Gene10	IFITM3	GZMK	IL7R	SLC22A4	IL7R	IL7R	RAB24	HSPA1B
Gene11	HSPA1B	DDX60L	PROK2	CD6	IFITM3	CYSTM1	S100A12	NFIL3
Gene12	SOD2	MCL1	CYSTM1	IL7R	CSF2RB	NFIL3	CCL5	S100A12
Gene13	IL1RN	SELL	MAL1	PLSCR1	IL1B	ACSL1	PLSCR1	ACSL1
Gene14	NAIP	LILRA5	KLRB1	PROK2	PROK2	SOD2	CD3D	FPR2
Gene15	CCR7	S100A12	RAB24	ACSL1	FCER1A	SLC22A4	ACSL1	FCER1A
Gene16	CCL5	HSPA1B	HSPA1B	KLRB1	FAIM3	LILRA5	ANXA3	RAB24
Gene17	FCGR1B	CSF2RB	CD3D	CSF2RB	PFKFB3	SP100	SP100	SLC22A4
Gene18	PROK2	IFITM3	ACSL1	ANXA3	FPR2	DDX60L	LRG1	LILRA5
Gene19	FFAR2	CD3D	FPR2	FPR2	C19ORF59	HSPA1B	NT5C3	NAIP
Gene20	NFIL3	TLR4	CCL5	IL1B	MAL1	IFITM1	PROK2	KLRB1
Gene21	SP100	FFAR2	SP100	SOD2	KLRB1	GZMK	IFITM1	SOD2
Gene22	S100A12	FAIM3	FFAR2	MCL1	NFIL3	NAIP	HSPA1B	IL7R
Gene23	CD3D	SOD2	IFITM3	FFAR2	DDX60L	CCL5	SLC22A4	IL1B
Gene24	SELL	FCER1A	CSF2RB	SP100	HSPA1B	S100A12	FPR2	SELL
Gene25	TLR4	PFKFB3	SLC22A4	NAIP	SELL	CCR7	IFITM3	ANXA3
Gene26	IL7R	IL1B	SELL	RAB24	SLC22A4	IL1B	FCER1A	PROK2
Gene27	CSF2RB	IFITM1	IFITM1	IFITM3	TLR4	FPR2	PFKFB3	GZMK
Gene28	IFITM1	CCR7	FAIM3	DDX60L	NAIP	PFKFB3	NAIP	PFKFB3
Gene29	DDX60L	C19ORF59	CCR7	S100A12	SOD2	FCER1A	TLR4	IFITM3
Gene30	ANXA3	KLRB1	DDX60L	IFITM1	CCL5	FAIM3	FFAR2	LRG1
Specificity	0.78	0.78	0.74	0.78	0.77	0.78	0.80	0.75
Sensitivity	0.90	0.93	0.94	0.90	0.91	0.91	0.90	0.91
AUC	0.91	0.90	0.91	0.91	0.91	0.91	0.90	0.91

Table 31 – Continued

Gene1	CYSTM1	DDX60L	FAIM3	FCER1A	FCGR1B	FFAR2	FPR2	GZMK
Gene2	PFKFB3	RAB24	FPR2	SOD2	ACSL1	IFITM3	CCR7	IL1RN
Gene3	IL1B	TLR4	PFKFB3	ACSL1	MAL1	IL1RN	SP100	SLC22A4
Gene4	PROK2	FFAR2	LILRA5	FCGR1B	CCR7	CCR7	C19ORF59	LRG1
Gene5	FCER1A	IFITM1	HSPA1B	CYSTM1	LRG1	C19ORF59	NAIP	IFITM1
Gene6	HSPA1B	MCL1	FFAR2	PFKFB3	C19ORF59	RAB24	IL1B	DDX60L
Gene7	SLC22A4	HSPA1B	C19ORF59	HSPA1B	IFITM1	FCGR1B	TLR4	CD3D
Gene8	FFAR2	ANXA3	GZMK	ANXA3	CCL5	ACSL1	SOD2	ACSL1
Gene9	CCL5	NFIL3	IL7R	RAB24	HSPA1B	S100A12	ANXA3	CSF2RB
Gene10	NAIP	LILRA5	ACSL1	LRG1	IL7R	KLRB1	S100A12	CCL5
Gene11	ACSL1	CCR7	CCL5	NAIP	PFKFB3	LILRA5	PFKFB3	CD6
Gene12	PLSCR1	CCL5	MAL1	CCL5	CSF2RB	IFITM1	IFITM3	C19ORF59
Gene13	KLRB1	NAIP	LRG1	TLR4	IL1RN	CCL5	RAB24	KLRB1
Gene14	IFITM1	SOD2	DDX60L	C19ORF59	SP100	SOD2	KLRB1	FCER1A
Gene15	NT5C3	ACSL1	SLC22A4	FFAR2	S100A12	NAIP	FCGR1B	SELL
Gene16	SOD2	KLRB1	IL1RN	CCR7	GZMK	PROK2	SLC22A4	CYSTM1
Gene17	SP100	IL1B	ANXA3	IL1B	NAIP	HSPA1B	IL7R	CCR7
Gene18	SELL	SP100	SP100	PROK2	CYSTM1	ANXA3	IL1RN	IFITM3
Gene19	CD6	PFKFB3	FCGR1B	NT5C3	SLC22A4	IL1B	FCER1A	LILRA5
Gene20	FPR2	LRG1	TLR4	MAL1	SOD2	DDX60L	PROK2	IL1B
Gene21	IFITM3	PROK2	IL1B	DDX60L	RAB24	SLC22A4	LILRA5	NAIP
Gene22	FCGR1B	GZMK	FCER1A	KLRB1	DDX60L	TLR4	CCL5	PROK2
Gene23	DDX60L	FCER1A	NAIP	PLSCR1	IL1B	NT5C3	MCL1	MAL1
Gene24	MAL1	IFITM3	IFITM1	LILRA5	IFITM3	IL7R	FFAR2	IL7R
Gene25	GZMK	MAL1	RAB24	CD6	FAIM3	MAL1	CYSTM1	FFAR2
Gene26	ANXA3	FCGR1B	SOD2	IFITM1	FPR2	SP100	PLSCR1	TLR4
Gene27	FAIM3	SLC22A4	S100A12	IFITM3	FFAR2	FCER1A	FAIM3	PFKFB3
Gene28	TLR4	CD6	PROK2	MCL1	LILRA5	PFKFB3	IFITM1	RAB24
Gene29	LRG1	CD3D	IFITM3	FAIM3	TLR4	FPR2	HSPA1B	HSPA1B
Gene30	C19ORF59	C19ORF59	CYSTM1	SP100	PROK2	CYSTM1	DDX60L	SP100
Specificity	0.79	0.78	0.79	0.79	0.78	0.79	0.73	0.79
Sensitivity	0.90	0.91	0.90	0.90	0.90	0.90	0.94	0.94
AUC	0.90	0.91	0.91	0.90	0.90	0.90	0.90	0.90

Table 31 – Continued

Gene1	HSPA1B	IFITM1	IFITM3	IL1B	IL1RN	IL7R	KLRB1	LILRA5
Gene2	CCL5	SLC22A4	PFKFB3	MAL1	NAIP	LRG1	IL1RN	IFITM1
Gene3	SLC22A4	FAIM3	IL7R	CCL5	FCGR1B	IL1B	IL7R	CYSTM1
Gene4	SELL	NAIP	IL1B	DDX60L	RAB24	MCL1	C19ORF59	PFKFB3
Gene5	CCR7	SOD2	NAIP	NAIP	CD3D	CCL5	CYSTM1	S100A12
Gene6	IFITM1	RAB24	C19ORF59	CSF2RB	IL1B	TLR4	SELL	MCL1
Gene7	CD3D	C19ORF59	DDX60L	FFAR2	LILRA5	CSF2RB	GZMK	IL1RN
Gene8	NAIP	KLRB1	SOD2	LILRA5	SP100	SLC22A4	FCER1A	FPR2
Gene9	LRG1	IL1B	ANXA3	CD6	SLC22A4	S100A12	DDX60L	C19ORF59
Gene10	NFIL3	HSPA1B	LRG1	TLR4	IFITM3	KLRB1	IFITM1	FAIM3
Gene11	DDX60L	CCR7	S100A12	KLRB1	KLRB1	RAB24	NFIL3	MAL1
Gene12	IL7R	LILRA5	NFIL3	CCR7	LRG1	IFITM3	SLC22A4	SOD2
Gene13	ANXA3	PLSCR1	MCL1	PFKFB3	FAIM3	SOD2	S100A12	KLRB1
Gene14	FAIM3	NFIL3	FCER1A	CYSTM1	PFKFB3	PFKFB3	TLR4	NAIP
Gene15	IL1B	CYSTM1	LILRA5	IFITM3	C19ORF59	HSPA1B	SP100	NT5C3
Gene16	SOD2	PFKFB3	SP100	IFITM1	GZMK	CCR7	CCR7	ACSL1
Gene17	PFKFB3	NT5C3	CCL5	FCGR1B	CSF2RB	ANXA3	ANXA3	CD3D
Gene18	IFITM3	S100A12	CYSTM1	SP100	FCER1A	DDX60L	IL1B	SP100
Gene19	GZMK	FCER1A	RAB24	FAIM3	SELL	FAIM3	FAIM3	PLSCR1
Gene20	TLR4	TLR4	SELL	RAB24	PLSCR1	FCER1A	PFKFB3	CCL5
Gene21	ACSL1	SP100	ACSL1	SELL	CYSTM1	SP100	CCL5	IL1B
Gene22	SP100	CSF2RB	PROK2	SLC22A4	FPR2	LILRA5	NAIP	CD6
Gene23	FFAR2	IL7R	FFAR2	S100A12	DDX60L	PROK2	HSPA1B	IL7R
Gene24	PLSCR1	ANXA3	TLR4	IL1RN	IFITM1	C19ORF59	RAB24	SELL
Gene25	C19ORF59	CCL5	PLSCR1	IL7R	IL7R	FCGR1B	FCGR1B	RAB24
Gene26	LILRA5	FPR2	SLC22A4	LRG1	HSPA1B	CD3D	ACSL1	IFITM3
Gene27	PROK2	MAL1	HSPA1B	PROK2	ANXA3	IFITM1	PROK2	TLR4
Gene28	CYSTM1	IFITM3	IL1RN	HSPA1B	ACSL1	FPR2	IFITM3	LRG1
Gene29	S100A12	ACSL1	IFITM1	SOD2	CCL5	NAIP	LILRA5	SLC22A4
Gene30	FCER1A	PROK2	CCR7	C19ORF59	TLR4	CYSTM1	LRG1	HSPA1B
Specificity	0.72	0.79	0.77	0.79	0.75	0.77	0.75	0.75
Sensitivity	0.96	0.93	0.91	0.91	0.94	0.90	0.96	0.94
AUC	0.90	0.90	0.90	0.90	0.90	0.91	0.90	0.90

Table 31 – Continued

Gene1	LRG1	MAL1	MCL1	NAIP	NFIL3	NT5C3	PFKFB3	PLSCR1
Gene2	KLRB1	ACSL1	PFKFB3	SLC22A4	DDX60L	IFITM3	CYSTM1	S100A12
Gene3	IL7R	MCL1	C19ORF59	IL7R	MAL1	FCER1A	NT5C3	NT5C3
Gene4	CYSTM1	CSF2RB	DDX60L	LRG1	CCL5	SELL	ACSL1	C19ORF59
Gene5	SOD2	S100A12	SOD2	CYSTM1	CSF2RB	KLRB1	IL1B	FCER1A
Gene6	FAIM3	NAIP	S100A12	CD3D	ACSL1	LILRA5	IL1RN	SLC22A4
Gene7	S100A12	FCER1A	CCL5	FCER1A	IFITM3	LRG1	C19ORF59	IFITM3
Gene8	FCER1A	LILRA5	FFAR2	IL1B	CD6	ACSL1	SP100	RAB24
Gene9	CD6	HSPA1B	CD6	IL1RN	SLC22A4	IFITM1	S100A12	CD6
Gene10	GZMK	DDX60L	FPR2	PFKFB3	IFITM1	IL7R	TLR4	SELL
Gene11	IL1B	KLRB1	IFITM3	SP100	FCGR1B	RAB24	PROK2	IFITM1
Gene12	TLR4	CYSTM1	NT5C3	KLRB1	MCL1	TLR4	FFAR2	GZMK
Gene13	C19ORF59	IL7R	CCR7	CCR7	LRG1	C19ORF59	CCL5	SOD2
Gene14	SLC22A4	SLC22A4	PLSCR1	CCL5	SP100	ANXA3	DDX60L	PROK2
Gene15	ACSL1	C19ORF59	LRG1	GZMK	RAB24	SLC22A4	SELL	NAIP
Gene16	CCL5	TLR4	IL1RN	SOD2	SOD2	FFAR2	FPR2	CCL5
Gene17	IFITM1	LRG1	RAB24	DDX60L	TLR4	PFKFB3	SOD2	LRG1
Gene18	PFKFB3	IFITM1	HSPA1B	ANXA3	PROK2	PROK2	HSPA1B	FPR2
Gene19	NT5C3	SOD2	FCER1A	PROK2	FFAR2	FPR2	GZMK	CCR7
Gene20	SELL	FPR2	CD3D	IFITM3	HSPA1B	FAIM3	LILRA5	IL1B
Gene21	SP100	PFKFB3	KLRB1	PLSCR1	C19ORF59	FCGR1B	MCL1	IL7R
Gene22	DDX60L	IL1B	FCGR1B	C19ORF59	PFKFB3	HSPA1B	IL7R	TLR4
Gene23	FPR2	CCL5	TLR4	HSPA1B	ANXA3	CD3D	NAIP	FFAR2
Gene24	HSPA1B	IFITM3	PROK2	SELL	FAIM3	CCL5	CCR7	PFKFB3
Gene25	FFAR2	FCGR1B	SP100	S100A12	NAIP	SOD2	PLSCR1	KLRB1
Gene26	IFITM3	SP100	IFITM1	TLR4	FCER1A	DDX60L	SLC22A4	HSPA1B
Gene27	CD3D	CCR7	LILRA5	FFAR2	S100A12	S100A12	IFITM3	ACSL1
Gene28	NAIP	GZMK	IL1B	IFITM1	IL1B	SP100	KLRB1	IL1RN
Gene29	MCL1	CD6	SLC22A4	FPR2	KLRB1	NAIP	LRG1	SP100
Gene30	PROK2	FFAR2	NAIP	ACSL1	CCR7	IL1B	IFITM1	DDX60L
Specificity	0.78	0.73	0.80	0.75	0.80	0.77	0.74	0.78
Sensitivity	0.91	0.94	0.90	0.93	0.87	0.93	0.94	0.93
AUC	0.91	0.91	0.90	0.91	0.91	0.91	0.91	0.91

Table 31 – Continued

Gene1	PROK2	RAB24	S100A12	SELL	SLC22A4	SOD2	SP100	TLR4
Gene2	CCL5	CCR7	FFAR2	PLSCR1	LRG1	CYSTM1	CD6	MAL1
Gene3	LILRA5	C19ORF59	ANXA3	GZMK	IL1B	HSPA1B	C19ORF59	CYSTM1
Gene4	PFKFB3	IFITM1	IFITM3	IFITM1	NAIP	IL7R	TLR4	MCL1
Gene5	ACSL1	HSPA1B	IL1B	CCL5	HSPA1B	ANXA3	FAIM3	ANXA3
Gene6	SLC22A4	FPR2	IFITM1	NAIP	S100A12	S100A12	HSPA1B	CSF2RB
Gene7	HSPA1B	LILRA5	C19ORF59	DDX60L	FCGR1B	LILRA5	IL7R	PFKFB3
Gene8	C19ORF59	FCGR1B	SOD2	SP100	IFITM3	CCL5	MAL1	ACSL1
Gene9	IL1B	KLRB1	FCGR1B	IL1RN	SP100	MAL1	ANXA3	DDX60L
Gene10	GZMK	CYSTM1	MCL1	TLR4	PFKFB3	C19ORF59	MCL1	IL1B
Gene11	ANXA3	FCER1A	LRG1	FFAR2	SELL	IFITM3	PFKFB3	FCER1A
Gene12	KLRB1	PROK2	TLR4	PROK2	NT5C3	FAIM3	LRG1	CD3D
Gene13	FCGR1B	FAIM3	KLRB1	PFKFB3	CD3D	TLR4	CD3D	LRG1
Gene14	LRG1	SP100	HSPA1B	FAIM3	C19ORF59	KLRB1	KLRB1	SLC22A4
Gene15	FCER1A	IL7R	PLSCR1	LRG1	ACSL1	IFITM1	RAB24	SOD2
Gene16	CYSTM1	PFKFB3	CCR7	C19ORF59	ANXA3	NT5C3	IFITM1	IFITM1
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Gene30	IL7R	SELL	NT5C3	IL1B	GZMK	FFAR2	S100A12	KLRB1
Specificity	0.78	0.74	0.79	0.80	0.80	0.77	0.74	0.79
Sensitivity	0.91	0.94	0.89	0.89	0.89	0.93	0.96	0.91
AUC	0.91	0.91	0.90	0.90	0.90	0.91	0.91	0.90

[00209] **Figure 4** shows boxplots representing 6 Models (A-F) which allow the stratification of septic/non septic patients. A predetermined cut off between Sepsis/non sepsis, indicated by the respective horizontal lines, is based on a decision rule for highest total accuracy achievable. For each model a training set based on 100 samples was created (left) and a blinded test of 61 samples was used to validate the models. The Models are:

- (A) using 40 genes and HPRT1 as normalization housekeeping gene.
- (B) using 8 genes and HPRT1 as normalization housekeeping gene.
- (C) using 40 genes and GAPDH as normalization housekeeping gene.
- (D) using 8 genes and GAPDH as normalization housekeeping gene.
- (E) using 40 genes and both HPRT1 and GAPDH as normalization housekeeping genes.
- (F) using 11 genes and both HPRT1 and GAPDH as normalization housekeeping genes.

[00210] Table 32 below shows the predictive value (AUC) of the 6 models described above for the respective number of genes (i.e. 40 genes, 8 genes, 40 genes, 8 genes, 40 genes, 11 genes), with HPRT1/GAPDH as the housekeeping gene.

Table 32: Predictive value (AUC) of the 6 models for the respective number of genes. Combined housekeeping gene indicates both HPRT1 and GAPDH.

No. of genes	Models	Area Under the Curve
40	HPRT1 Housekeeping gene	0.928
8	HPRT1 Housekeeping gene	0.94
40	GAPDH Housekeeping gene	0.927
8	GAPDH Housekeeping gene	0.94
40	Combined Housekeeping gene	0.927
11	Combined Housekeeping gene	0.941

[00211] **Figure 5** shows a boxplot representing 85 sepsis patients based on either 37 genes(A) or 14 genes(B). Weight scoring system was implemented using 2 models which allow the segregation of severe sepsis from mild sepsis.

[00212] **Figure 6** shows an average plasma protein concentration (S100A12) in patients selected from the group consisting of control, infection, mild sepsis and severe sepsis/septic shock, indicating a correlation between severity of Sepsis and protein concentration.

[00213] Advantageously, the methods, biomarker or biomarkers and kits described can be used for the early detection and diagnosis of sepsis, and also the monitoring of patients for an improvement of treatment and outcome for such patients.

7. Advantageously, the methods, biomarker or biomarkers and kits described can be used to identify and/or classify a subject or patient as a candidate for sepsis therapy.

Diagnostic kits

[00214] Detection kits may contain antibodies, aptamers, amplification systems, detection reagents (chromogen, fluorophore, etc), dilution buffers, washing solutions, counter stains or any combination thereof. Kit components may be packaged for either manual or partially or wholly automated practice of the foregoing methods. In other embodiments involving kits, this invention contemplates a kit including compositions of the present invention, and optionally

instructions for their use. Such kits may have a variety of uses, including, for example, stratifying patient populations, diagnosis, prognosis, guiding therapeutic treatment decisions, and other applications.

[00215] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. The invention includes all such variation and modifications. The invention also includes all of the steps, features, formulations and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

[00216] Each document, reference, patent application or patent cited in this text is expressly incorporated herein in their entirety by reference, which means that it should be read and considered by the reader as part of this text. That the document, reference, patent application or patent cited in this text is not repeated in this text is merely for reasons of conciseness.

[00217] Any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

[00218] The present invention is not to be limited in scope by any of the specific embodiments described herein. These embodiments are intended for the purpose of exemplification only. Functionally equivalent products, formulations and methods are clearly within the scope of the invention as described herein.

[00219] The invention described herein may include one or more range of values (e.g. size, concentration etc). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range which lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range.

[00220] Throughout this specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be

understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. It is also noted that in this disclosure and particularly in the claims and/or paragraphs, terms such as “comprises”, “comprised”, “comprising” and the like can have the meaning attributed to it in U.S. Patent law; e.g., they can mean “includes”, “included”, “including”, and the like; and that terms such as “consisting essentially of” and “consists essentially of” have the meaning ascribed to them in U.S. Patent law, e.g., they allow for elements not explicitly recited, but exclude elements that are found in the prior art or that affect a basic or novel characteristic of the invention.

[00221] Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

[00222] Other features, benefits and advantages of the present invention not expressly mentioned above can be understood from this description by those skilled in the art.

[00223] Although the foregoing invention has been described in some detail by way of illustration and example, and with regard to one or more embodiments, for the purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the novel teachings and advantages of this invention that certain changes, variations and modifications may be made thereto without departing from the spirit or scope of the invention as described.

[00224] It would be further appreciated that although the invention covers individual embodiments, it also includes combinations of the embodiments discussed. For example, the features described in one embodiment is not being mutually exclusive to a feature described in another embodiment, and may be combined to form yet further embodiments of the invention.

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 <213> Homo sapiens formyl peptide receptor 2 (FPR2)

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 <212> DNA
 <213> Homo sapiens heat shock 70kDa protein 1B (HSPA1B)

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<210> 11
<211> 733
<212> DNA
<213> Homo sapiens interferon induced transmembrane protein 1 (IFITM1)

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<210> 12
<211> 678
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<210> 13
<211> 1498
<212> DNA

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<213> Homo sapiens interleukin 1, beta (IL1B)

<400> 13

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<210> 14

<211> 1794

<212> DNA

<213> Homo sapiens interleukin 1 receptor antagonist (IL1RN)

<400> 14

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<210> 15

<211> 1363

<212> DNA

<213> Homo sapiens leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 5 (LILRA5)

<400> 15

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<210> 16

<211> 1780

<212> DNA

<213> Homo sapiens leucine-rich alpha-2-glycoprotein 1 (LRG1)

<400> 16

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<211> 466

<212> DNA

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<211> 2442

<212> DNA

<213> Homo sapiens selectin L (SELL)

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<211> 2214

<212> DNA

<213> Homo sapiens solute carrier family 22 (organic cation/ergothioneine transporter), member 4 (SLC22A4)

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<211> 1593

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<211> 5661

<212> DNA

<213> Homo sapiens toll-like receptor 4 (TLR4)

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<212> DNA

<213> Homo sapiens Fas apoptotic inhibitory molecule 3 (FAIM3)

<400> 35

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<210> 36

<211> 1198

<212> DNA

<213> Homo sapiens Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide (FCER1A)

<400> 36

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<210> 38
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 <212> DNA
 <213> Homo sapiens interleukin 7 receptor (IL7R)

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<210> 39
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<213> Homo sapiens killer cell lectin-like receptor subfamily B, member 1
(KLRB1)

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<213> Homo sapiens mal, T-cell differentiation protein (MAL)

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<213> Homo sapiens hypoxanthine phosphoribosyltransferase 1 (HPRT1)

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CLAIMS

1. An *in vitro* method of detecting or predicting sepsis in a subject, the method comprising:
 - i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
 - ii. comparing the level measured to a reference level of a corresponding biomarker,wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 34, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity, ; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), or (b),
wherein a difference between the level measured in the first sample and the reference level is indicative of sepsis being present in the first sample.
2. The method of claim 1, wherein the at least one biomarker comprises two or more biomarkers wherein the second or subsequent biomarker is not the same as the first biomarker and is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23,

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3. The method of claim 1 or 2, wherein the presence of sepsis is determined by detecting in the subject an increase in the level of the at least one biomarker measured in the first sample, the at least one biomarker selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a) or (b), as compared to the reference level of the corresponding biomarker.
4. The method of claim 2, wherein the presence of sepsis is determined by detecting in the subject an increase in the second or subsequent biomarker measured in the first sample, the second or subsequent biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID

NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a) or, (b), as compared to the reference level of the corresponding biomarker.

5. The method of claim 1 or 2, wherein the presence of sepsis is determined by detecting in the subject a decrease in the level of the at least one biomarker measured in the first sample, the at least one biomarker selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 34, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a) or (b), as compared to the reference level of the corresponding biomarker.
6. The method of claim 2, wherein the presence of sepsis is determined by detecting in the subject a decrease in the level of the second or subsequent biomarker measured in the first sample, the second or subsequent biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding

amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), or (b), as compared to the reference level of the corresponding biomarker.

7. The method of any one of the preceding claim, wherein the reference level is the level of the corresponding biomarker in a second sample isolated from at least one subject with no sepsis.
8. The method of any one of the preceding claims, wherein the comparing step comprises applying a decision rule to determine or predict the presence or absence of sepsis in the subject.
9. An *in vitro* method of detecting or predicting whether a subject has one of a plurality of conditions selected from a group consisting of: a control, unrelated to any infective cause, or non-infected systemic inflammatory response syndrome (SIRS); infection; and sepsis including mild sepsis, severe sepsis, or septic shock, the method comprising:
 - i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
 - ii. comparing the level measured to a reference level of a corresponding biomarker,wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 34, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity, ; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), or (b),

wherein the level measured in the first sample is statistically substantially similar to the reference level is indicative of whether the subject has one of the conditions.

10. The method of claim 9, wherein the at least one biomarker comprises two or more biomarkers wherein the second or subsequent biomarker is not the same as the first biomarker and is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a) or (b).
11. The method of claim 9 or 10, wherein the reference level is the level of a corresponding biomarker in a second sample isolated from at least one subject selected from a group consisting of: a control subject unrelated to any infective cause, or non-infected systemic inflammatory response syndrome (SIRS);, an infection positive subject; and a sepsis subject including a mild sepsis positive subject, a severe sepsis positive subject or a septic shock positive subject.

12. The method of any one of claims 9-11, wherein the comparing step comprises applying a decision rule to determine or predict whether the subject has one of the conditions.
13. A kit for detecting or predicting sepsis in a subject, the kit consisting of:
- i. a first reagent capable of specifically binding to a first biomarker selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 34, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a);
 - ii. a second or subsequent reagent capable of specifically binding to a second or subsequent biomarker not the same as the first biomarker and is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; and (b) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a);
 - iii. reagents for a sample processing or sample preparation;

- iv. detection reagents; and
 - v. additional reagent capable of specifically binding a reference biomarker.
- 14. The kit of claim 13, wherein the first reagent and the second or subsequent reagent comprises a primer pair capable of specifically binding to a portion of the first and second or subsequent biomarkers.
- 15. The kit of claim 13 or 14, wherein the reference biomarker comprises a normalization housekeeping gene.
- 16. The kit of claim 13 or 14, wherein the reference biomarker comprises a corresponding biomarker to the first and second or subsequent biomarkers.
- 17. The Kit of any one of claims 13 to 16, wherein the first and the second or subsequent reagent capable of specifically binding to the first and the second or subsequent biomarker in (i) and (ii) have a set of 5 or 10 or 20 or 30 or 40 reagents capable of specifically binding to the first and the second or subsequent biomarkers.
- 18. A kit for detecting or predicting sepsis in a subject, consisting of:
 - a. a first antibody capable of binding selectively to a biomarker selected from a group consisting of: a polypeptide encoded by a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 34, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity;
 - b. a second or subsequent antibody capable of specifically binding to a second or subsequent biomarker not the same as the first biomarker and is selected from a group consisting of: a polypeptide encoded by a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4,

SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity;

- c. reagents for a sample processing or preparation;
 - d. reagents for detection of a complex formed between the first and second or subsequent antibodies and a complement component of the biomarker, and
 - e. an additional antibody capable of specifically binding a reference biomarker.
19. The kit of claim 18, wherein the reference biomarker comprises a corresponding biomarker in a second sample isolated from at least one subject with no sepsis.
20. The kit of claim 18, wherein the additional antibody capable of specifically binding a reference biomarker comprises a normalization housekeeping gene.
21. The kit of claim 18, wherein the reference biomarker comprises a corresponding biomarker in a second sample isolated from at least one subject selected from a group consisting of: a healthy control subject, a control subject having a condition unrelated to any infective cause, a non-infected SIRS positive subject, an infection positive subject; and a sepsis subject including, a mild sepsis positive subject, a severe sepsis positive subject and a septic shock positive subject.

22. The kit of any one of claims 18 to 21, wherein the first and the second or subsequent antibody capable of specifically binding to the first and the second or subsequent biomarker in (a) and (b) have a set of 5 or 10 or 20 or 30 or 40 antibodies capable of specifically binding to the first and the second or subsequent biomarkers.
23. An *in vitro* method of detecting or predicting sepsis in a subject, the method comprising:
- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
 - ii. comparing the level measured to a reference level of a corresponding biomarker,
- wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 34, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity;; (b) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one or more of the sequences of (a), or (b),
- wherein a difference between the level measured in the first sample and the reference level is indicative of sepsis being present in the first sample.
24. The method of claim 23, wherein the at least one biomarker comprises two or more biomarkers wherein the second or subsequent biomarker is not the same as the first biomarker and is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO:

5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a) or (b).

25. An *in vitro* method of detecting or predicting whether a subject has one of a plurality of conditions selected from a group consisting of: a control, unrelated to any infective cause, or non-infected systemic inflammatory response syndrome (SIRS); infection; mild sepsis; and severe sepsis including septic shock, the method comprising:

- i. measuring the level of at least one biomarker in a first sample isolated from the subject; and
- ii. comparing the level measured to a reference level of a corresponding biomarker,

wherein the at least one biomarker is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 12, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 34, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one or more, and in any combination, of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence

capable of hybridising selectively to any one or more of the sequences of (a), or (b),

wherein the level measured in the first sample is statistically substantially similar to the reference level is indicative of whether the subject has one of the conditions.

26. The method of claim 25, wherein the at least one biomarker comprises two or more biomarkers wherein the second or subsequent biomarker is not the same as the first biomarker and is selected from a group consisting of: (a) a polynucleotide comprising a nucleotide sequence set forth in any one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, or a fragment comprising at least 90% nucleotide sequence identity; (b) a polynucleotide comprising a nucleotide sequence set forth in any one of the sequences of (a), that encodes a polypeptide comprising the corresponding amino acid sequence; and (c) a polynucleotide comprising a nucleotide sequence capable of hybridising selectively to any one of the sequences of (a), or (b).