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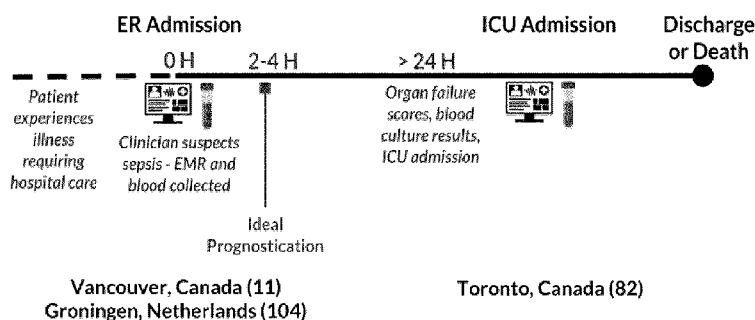


FIG. 1

(57) Abstract: The present disclosure relates to methods for classifying a subject into a sepsis mechanistic endotype as well as methods for predicting severity of sepsis in a subject. The methods can comprise use of a biological sample obtained from the subject at first clinical presentation. The classification of the subject into a sepsis mechanistic endotype and/or prediction of severity of sepsis may, for example, allow for treatment of sepsis using an approach suitable to the particular mechanistic endotype and/or severity.

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DIAGNOSTIC FOR SEPSIS ENDOTYPES AND/OR SEVERITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] The present application claims the benefit of priority from co-pending U.S. provisional application no. 63/192,746 filed on May 25, 2021, the contents of which are incorporated herein by reference in their entirety.

FIELD

[002] The present disclosure relates to the field of biomarkers for sepsis. For example, the present disclosure relates to a unique set of DNA sequences that, may for example, enable the separation of sepsis patients into distinct mechanistic and/or clinically meaningful clusters, as well as the prediction of sepsis severity and mortality at first clinical presentation.

BACKGROUND

[003] Sepsis continues to be the major infection-related cause of death globally, leading to an estimated 19.7% of deaths (e.g., 11 million deaths in 2017) annually. More recently sepsis has been recognized to be the major cause of mortality in patients with severe Covid-19 infections. Despite advances in modern medicine including new antibiotics and vaccines, earlier recognition and best practice treatments, and efficient well-equipped intensive care units, there is a high rate of mortality, about 22%, that has remained little changed for decades.

[004] Sepsis is described as a dysfunctional, life-threatening response to infection and is extremely common (estimated 48.9 million cases leading to 11 million annual deaths in 2017). Inter-individual clinical variability in the course of early sepsis can prevent clinicians from appropriately triaging patients for optimal treatment. Identifying gene expression signatures capturing specific host responses in ER and ICU patients may, for example, allow clinicians to identify the most at-risk groups of patients, provide early diagnostic certainty and enable appropriate use of antibiotics and development of disease-specific therapies, as well as identifying patients who likely do not need such intensive treatment, thus reducing costs and saving hospital resources.

[005] Sepsis is notorious for the clinical heterogeneity observed in patients, who often demonstrate broad and fairly non-specific symptomology in the emergency room (ER), and can rapidly deteriorate thereafter. Therefore, it is difficult for clinicians to appropriately detect and triage sepsis patients early on in the disease course. The general doctrine that each hour's delay in initiating antibiotics costs lives, is still accepted by clinicians, often by initiating early treatment with potent antibiotics in the hope that the progression to sepsis is

hindered. The problem is that some patients who will go on to severe sepsis are not recognized early enough while others that do not have sepsis will be treated incorrectly. The latter has the downside of contributing to the rise of antibiotic resistance, since broad-spectrum antibiotics are overused even in cases where there is no bacterial infection. Thus, a novel means of triaging sepsis patients is desirable, given the rapid deterioration and the societal repercussions of increased antibiotic resistance and health care costs.

[006] Biomarkers for the diagnosis of sepsis have been proposed in U.S. Patent No. 7,767,395; U.S. Patent No 8,029,982, U.S. Patent Application Publication No. 2011/0312521; U.S. Patent Application Publication No. 2011/0076685; U.S. Patent Application Publication No. 2020/0140948A1, International Patent Application Publication No. WO 2013/152047, International Patent Application Publication No. WO 2014/209238, International Patent Application Publication No. WO 2015/135071A1, International Patent Application No. WO 2018/146162A1, and International Patent Application Publication No. WO 2016/145426A1.

[007] Blood transcriptomics has proven useful in obtaining systems-level representations of the responses dysregulated during sepsis. Using this method, several groups have identified, either in the ER or ICU, gene expression signatures that discriminate between sepsis and Systemic Inflammatory Response Syndrome (SIRS), or between patients who survive or succumb [Pena OM, et al. *EBioMedicine*. 2014;1:64-71, doi:10.1016/j.ebiom.2014.10.003; McHugh L, et al. *PLoS Medicine* 2015;12:e1001916 doi:10.1371/journal.pmed.1001916; Sweeney TE, et al. *Science Transl. Med.* 2015;7:287ra71. doi:10.1126/scitranslmed.aaa5993; Scicluna BP, et al. *Amer. J. Resp. Crit. Care Medi.* 2015;192:826-835. doi:10.1164/rccm.201502-0355OC]. Nevertheless, these approaches typically lack sensitivity because of substantial heterogeneity in patients with similar outcomes that is not considered. This includes but is not limited to responses driven by individual genetic variation, demographic factors, the infection source and agent, appropriateness of therapeutic intervention, comorbidities including pre-existing immune-suppressive conditions, and/or epigenetics [Leligdowicz A, and Matthay MA. *Critical Care* 23:80, doi:10.1186/s13054-019-2372-2]. These shortcomings have led to sepsis being reframed as a condition comprised of several subgroups termed endotypes, which represent distinct biologically-driven and clinically-relevant groups of patients with varied severity and clinical outcomes, where endotypes are defined as subtypes of a condition, defined by distinct functional and/or pathobiological mechanisms. Specifically, endotypes may provide more

sensitive markers enabling risk-stratification and opportunities for individualized therapies. However, endotypes in sepsis have only been characterized in patients with advanced disease, while early prognostication of endotype status is desirable.

[008] Framing sepsis in the context of endotypes has the potential to identify dysregulation of biological processes common to subgroups, thus enabling endotype-specific treatment of patients in a specific host-directed (e.g., immunomodulatory) manner. Previous research identifying endotypes has shown that subgroups of patients exist in sepsis patients, particularly in those who present to intensive care units (ICU) [Scicluna BP et al. *Lancet Resp. Med.*. 2017;5:816-826. doi:10.1016/S2213-2600(17)30294-1; Davenport EE, et al. *The Lancet Resp. Med.* 2016;4:259-271. doi:10.1016/S2213-2600(16)00046-1; Maslove DM, et al. *Critical Care.* 2012;16:R183. doi:10.1186/cc11667; Sweeney TE, et al. *Critical Care Med.* 2018;46:915-925. doi:10.1097/CCM.0000000000003084], but have not addressed patients just entering the emergency room (ER) at first clinical presentation.

[009] The molecular responses determining endotype status have often been explained by the influence of several immune cell types, most notably neutrophils, monocytes, and T cell subsets that bear the features of immunosuppression [Hotchkiss RS et al. *Lancet Infect. Dis.* 2013;13:260-8. doi:10.1016/S1473-3099(13)70001-X]. To date the published studies demonstrate generally that there are endotypes identifiable after sepsis has already been confirmed. However, this represents a stage in a patient's clinical course where prognosis is arguably less useful, since patients have already deteriorated and likely already require intensive care and antibiotics. Moreover, there is little consensus as to the make-up and nature of endotypes.

[0010] This background information is provided for the purpose of making known information believed by the applicant to be of possible relevance to the present invention. No admission is necessarily intended, nor should be construed, that any of the preceding information constitutes prior art against the present invention.

SUMMARY

[0011] An objective of the present disclosure was to identify endotypes at first clinical presentation, where patients show broad clinical traits and final sepsis diagnoses are not established. Whole blood and clinical data profiles were collected from 115 patients in emergency rooms and 82 patients in one intensive care unit, and compared to 9 healthy controls from the same sources. ER patients were recruited into the study within two hours of admission if the attending clinician suspected possible sepsis and observed two or more systemic

inflammatory response syndrome (SIRS) symptoms. Blood RNA-Seq transcriptomic profiles were analyzed to identify early mechanistic gene expression signatures useful for triage. Machine learning was used to uncover endotypes (subdivisions of the disease with distinct pathophysiological mechanisms and clinical responses) and to validate corresponding gene signatures with prognostic value. Patients with early sepsis exhibited evidence of five mechanistically distinct endotypes, namely Neutrophilic-Suppressive (NPS), Inflammatory (INF), Innate Host Defense (IHD), Interferon (IFN), and Adaptive (ADA) endotypes. Subsequently, a classification tool employing 88 genes was used to accurately predict endotype status in a validation cohort while another 247 showed suitable differential expression in the given endotypes to be useful in differentiation between endotypes. This included 82 ICU patients, of which 27 patients had Covid-19-mediated sepsis. Subsets of these 88 genes can be used, for example, to accurately identify specific endotypes (including those causing higher severity), through gene expression analysis of patient blood. Across all patients, the NPS and INF endotypes showed the worse prognosis, with higher organ dysfunction scores and severity. Furthermore, a predictive severity signature was demonstrated. This provides a method to triage a diverse spectrum of prospective pre-diagnosis sepsis patients in the emergency room (ER) into 5 mechanism-based endotypes based on the underlying molecular responses, and shows that endotypes are associated with specific clinical characteristics and outcomes. These endotypes remain detectable in the intensive care unit (ICU), indicating they are stable. The separation of patients into endotypes has prognostic value and can inform a physician regarding future severity, enabling only the worst afflicted patients to receive the most intensive treatments and driving the potential for personalized medicines. Furthermore, signatures predicting enhanced severity independent of endotype status are described.

[0012] Accordingly, the present disclosure includes a method for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype, wherein the sample gene signature and reference gene signature comprise an NPS endotype sub-signature, an INF endotype sub-signature, an IHD endotype sub-signature, an IFN endotype sub-signature, an ADA endotype sub-signature or combinations thereof, wherein the NPS endotype sub-signature comprises genes selected from

the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, and XCR1; wherein the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYPA, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC4A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, and YPEL4; wherein the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, and TRIM2; wherein the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, and

LAMP3; and wherein the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, USP18, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, and TTC21A.

[0013] In an embodiment, the reference gene signature represents a standard level of expression of the genes comprised therein and a difference between a sample endotype sub-signature and a reference endotype sub-signature indicates that the subject has the sepsis mechanistic endotype corresponding to that sub-signature.

[0014] In an embodiment, the sample gene signature and the reference gene signature comprise the NPS endotype sub-signature, the INF endotype sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, and the ADA endotype sub-signature.

[0015] In an embodiment, the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In another embodiment, the NPS endotype sub-signature comprises: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19.

[0016] In an embodiment, the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In another embodiment, the INF endotype sub-signature comprises: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2.

[0017] In an embodiment, the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In another embodiment, the IHD endotype sub-signature comprises: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34,

GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600.

[0018] In an embodiment, the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In another embodiment, the IFN endotype sub-signature comprises: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC.

[0019] In an embodiment, the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, and USP18. In another embodiment, the ADA endotype sub-signature comprises: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1 and USP18.

[0020] The present disclosure also includes a method for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype, wherein the sample gene signature and reference gene signature comprise an NPS endotype signature pair, an INF endotype signature pair, an IHD endotype signature pair, an IFN endotype signature pair, an ADA endotype signature pair or combinations thereof, wherein the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, MLLT1/KLF14, ADAMTS3/PCOLCE2, ADAMTS3/ZDHHC19, ADAMTS3/SLC51A, ADAMTS3/HPGD, ADAMTS3/SEMA6B, ADAMTS3/EFNA1, ADAMTS3/AGFG1, ADAMTS3/NSUN7, ADAMTS3/TNFAIP8L3, ADAMTS3/KREMEN1, ADAMTS3/ORM2, ADAMTS3/MIR646HG, ADAMTS3/KLF14, AGFG1/NSUN7, AGFG1/TNFAIP8L3, AGFG1/KREMEN1, AGFG1/ORM2, AGFG1/MIR646HG, AGFG1/KLF14,

ANXA3/GPR84, ANXA3/OLAH, ANXA3/ADAMTS3, ANXA3/PCOLCE2,
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 IL1R1/GPR84, IL1R1/OLAH, IL1R1/ADAMTS3, IL1R1/PCOLCE2, IL1R1/ZDHHC19,
 IL1R1/SLC51A, IL1R1/HPGD, IL1R1/SEMA6B, IL1R1/EFNA1, IL1R1/AGFG1,

IL1R1/NSUN7, IL1R1/TNFAIP8L3, IL1R1/KREMEN1, IL1R1/ORM2, IL1R1/MIR646HG, IL1R1/KLF14, KREMEN1/ORM2, KREMEN1/MIR646HG, KREMEN1/KLF14, MIR646HG/KLF14, MLLT1/ANXA3, MLLT1/GPR84, MLLT1/OLAH, MLLT1/ADAMTS3, MLLT1/PCOLCE2, MLLT1/ZDHHC19, MLLT1/SLC51A, MLLT1/HPGD, MLLT1/SEMA6B, MLLT1/EFNA1, MLLT1/AGFG1, MLLT1/NSUN7, MLLT1/TNFAIP8L3, MLLT1/KREMEN1, MLLT1/ORM2, MLLT1/MIR646HG, MLLT1/KLF14, NSUN7/TNFAIP8L3, NSUN7/KREMEN1, NSUN7/ORM2, NSUN7/MIR646HG, NSUN7/KLF14, OLAH/ADAMTS3, OLAH/PCOLCE2, OLAH/ZDHHC19, OLAH/SLC51A, OLAH/HPGD, OLAH/SEMA6B, OLAH/EFNA1, OLAH/AGFG1, OLAH/NSUN7, OLAH/TNFAIP8L3, OLAH/KREMEN1, OLAH/ORM2, OLAH/MIR646HG, OLAH/KLF14, ORM2/MIR646HG, ORM2/KLF14, PCOLCE2/ZDHHC19, PCOLCE2/SLC51A, PCOLCE2/HPGD, PCOLCE2/SEMA6B, PCOLCE2/EFNA1, PCOLCE2/AGFG1, PCOLCE2/NSUN7, PCOLCE2/TNFAIP8L3, PCOLCE2/KREMEN1, PCOLCE2/ORM2, PCOLCE2/MIR646HG, PCOLCE2/KLF14, PFKFB2/MLLT1, PFKFB2/ANXA3, PFKFB2/GPR84, PFKFB2/OLAH, PFKFB2/ADAMTS3, PFKFB2/PCOLCE2, PFKFB2/ZDHHC19, PFKFB2/SLC51A, PFKFB2/HPGD, PFKFB2/SEMA6B, PFKFB2/EFNA1, PFKFB2/AGFG1, PFKFB2/NSUN7, PFKFB2/TNFAIP8L3, PFKFB2/KREMEN1, PFKFB2/ORM2, PFKFB2/MIR646HG, PFKFB2/KLF14, SEMA6B/EFNA1, SEMA6B/AGFG1, SEMA6B/NSUN7, SEMA6B/TNFAIP8L3, SEMA6B/KREMEN1, SEMA6B/ORM2, SEMA6B/MIR646HG, SEMA6B/KLF14, SLC51A/HPGD, SLC51A/SEMA6B, SLC51A/EFNA1, SLC51A/AGFG1, SLC51A/NSUN7, SLC51A/TNFAIP8L3, SLC51A/KREMEN1, SLC51A/ORM2, SLC51A/MIR646HG, SLC51A/KLF14, TNFAIP8L3/KREMEN1, TNFAIP8L3/ORM2, TNFAIP8L3/MIR646HG, TNFAIP8L3/KLF14, ZDHHC19/SLC51A, ZDHHC19/HPGD, ZDHHC19/SEMA6B, ZDHHC19/EFNA1, ZDHHC19/AGFG1, ZDHHC19/NSUN7, ZDHHC19/TNFAIP8L3, ZDHHC19/KREMEN1, ZDHHC19/ORM2, ZDHHC19/MIR646HG, and ZDHHC19/KLF14; wherein the INF endotype signature pair is selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, SPTA1/FECH, ANKRD22/GLRX5, ANKRD22/GYP A, ANKRD22/IFIT1B, ANKRD22/ITLN1, ANKRD22/KLHDC8A, ANKRD22/RHCE, ANKRD22/RNF182, ANKRD22/SPTA1, ANKRD22/THEM5, ANKRD22/TSPAN5, APOL4/BNIP3L, APOL4/CA1, APOL4/DYRK3, APOL4/FAM83A, APOL4/GLRX5,

APOL4/GYP A, APOL4/IFIT1B, APOL4/ITLN1, APOL4/KLHDC8A, APOL4/RHAG,
 APOL4/RHCE, APOL4/RIOK3, APOL4/RNF182, APOL4/SPTA1, APOL4/THEM5,
 APOL4/TLCD4, APOL4/TMCC2, APOL4/TSPAN5, APOL4/TSPO2, BNIP3L/ANKRD22,
 BNIP3L/CA1, BNIP3L/CARD17, BNIP3L/CD274, BNIP3L/DYRK3, BNIP3L/FAM83A,
 BNIP3L/GBP5, BNIP3L/GLRX5, BNIP3L/GYP A, BNIP3L/IFIT1B, BNIP3L/ITLN1,
 BNIP3L/KLHDC8A, BNIP3L/P2RY14, BNIP3L/RHAG, BNIP3L/RHCE, BNIP3L/RNF182,
 BNIP3L/SPTA1, BNIP3L/TFEC, BNIP3L/THEM5, BNIP3L/TLCD4, BNIP3L/TMCC2,
 BNIP3L/TSPAN5, BNIP3L/TSPO2, CA1/ANKRD22, CA1/CARD17, CA1/DYRK3,
 CA1/FAM83A, CA1/GBP5, CA1/GLRX5, CA1/GYP A, CA1/IFIT1B, CA1/ITLN1,
 CA1/KLHDC8A, CA1/P2RY14, CA1/RHCE, CA1/RNF182, CA1/SPTA1, CA1/THEM5,
 CA1/TLCD4, CA1/TSPAN5, CD274/CA1, CD274/DYRK3, CD274/FAM83A,
 CD274/GLRX5, CD274/GYP A, CD274/IFIT1B, CD274/ITLN1, CD274/KLHDC8A,
 CD274/RHCE, CD274/RNF182, CD274/SPTA1, CD274/THEM5, CD274/TLCD4,
 CD274/TMCC2, CD274/TSPAN5, DYRK3/ANKRD22, DYRK3/CARD17,
 DYRK3/FAM83A, DYRK3/GBP5, DYRK3/GLRX5, DYRK3/GYP A, DYRK3/IFIT1B,
 DYRK3/ITLN1, DYRK3/KLHDC8A, DYRK3/P2RY14, DYRK3/RHCE, DYRK3/RNF182,
 DYRK3/SPTA1, DYRK3/THEM5, DYRK3/TLCD4, DYRK3/TSPAN5,
 FAM83A/ANKRD22, FAM83A/CARD17, FAM83A/GBP5, FAM83A/GLRX5,
 FAM83A/GYP A, FAM83A/IFIT1B, FAM83A/ITLN1, FAM83A/KLHDC8A,
 FAM83A/P2RY14, FAM83A/RHCE, FAM83A/RNF182, FAM83A/SPTA1,
 FAM83A/THEM5, FAM83A/TLCD4, FAM83A/TSPAN5, FECH/ANKRD22,
 FECH/APOL4, FECH/BNIP3L, FECH/CA1, FECH/CARD17, FECH/CD274,
 FECH/DYRK3, FECH/FAM83A, FECH/GBP5, FECH/GLRX5, FECH/GYP A,
 FECH/IFIT1B, FECH/ITLN1, FECH/KLHDC8A, FECH/P2RY14, FECH/RHAG,
 FECH/RHCE, FECH/RIOK3, FECH/RNF182, FECH/SPTA1, FECH/TFEC, FECH/THEM5,
 FECH/TLCD4, FECH/TMCC2, FECH/TSPAN5, FECH/TSPO2, GBP5/GLRX5,
 GBP5/GYP A, GBP5/IFIT1B, GBP5/ITLN1, GBP5/KLHDC8A, GBP5/RHCE,
 GBP5/RNF182, GBP5/SPTA1, GBP5/THEM5, GBP5/TSPAN5, GLRX5/CARD17,
 GLRX5/IFIT1B, GLRX5/RHCE, GLRX5/THEM5, GYP A/CARD17, GYP A/GLRX5,
 GYP A/IFIT1B, GYP A/ITLN1, GYP A/P2RY14, GYP A/RHCE, GYP A/RNF182,
 GYP A/THEM5, IFIT1B/CARD17, ITLN1/CARD17, ITLN1/GLRX5, ITLN1/IFIT1B,
 ITLN1/RHCE, ITLN1/RNF182, ITLN1/THEM5, KLHDC8A/CARD17, KLHDC8A/GLRX5,
 KLHDC8A/GYP A, KLHDC8A/IFIT1B, KLHDC8A/ITLN1, KLHDC8A/P2RY14,

KLHDC8A/RHCE, KLHDC8A/RNF182, KLHDC8A/SPTA1, KLHDC8A/THEM5, KLHDC8A/TSPAN5, P2RY14/GLRX5, P2RY14/IFIT1B, P2RY14/ITLN1, P2RY14/RHCE, P2RY14/RNF182, P2RY14/THEM5, RHAG/ANKRD22, RHAG/CA1, RHAG/CARD17, RHAG/CD274, RHAG/DYRK3, RHAG/FAM83A, RHAG/GBP5, RHAG/GLRX5, RHAG/GYP A, RHAG/IFIT1B, RHAG/ITLN1, RHAG/KLHDC8A, RHAG/P2RY14, RHAG/RHCE, RHAG/RNF182, RHAG/SPTA1, RHAG/THEM5, RHAG/TLCD4, RHAG/TMCC2, RHAG/TSPAN5, RHAG/TSPO2, RHCE/CARD17, RHCE/IFIT1B, RHCE/THEM5, RIOK3/ANKRD22, RIOK3/BNIP3L, RIOK3/CA1, RIOK3/CARD17, RIOK3/CD274, RIOK3/DYRK3, RIOK3/FAM83A, RIOK3/GBP5, RIOK3/GLRX5, RIOK3/GYP A, RIOK3/IFIT1B, RIOK3/ITLN1, RIOK3/KLHDC8A, RIOK3/P2RY14, RIOK3/RHAG, RIOK3/RHCE, RIOK3/RNF182, RIOK3/SPTA1, RIOK3/TFEC, RIOK3/THEM5, RIOK3/TLCD4, RIOK3/TMCC2, RIOK3/TSPAN5, RIOK3/TSPO2, RNF182/CARD17, RNF182/GLRX5, RNF182/IFIT1B, RNF182/RHCE, RNF182/THEM5, SPTA1/CARD17, SPTA1/GLRX5, SPTA1/GYP A, SPTA1/IFIT1B, SPTA1/ITLN1, SPTA1/P2RY14, SPTA1/RHCE, SPTA1/RNF182, SPTA1/THEM5, SPTA1/TSPAN5, TFEC/CA1, TFEC/DYRK3, TFEC/FAM83A, TFEC/GLRX5, TFEC/GYP A, TFEC/IFIT1B, TFEC/ITLN1, TFEC/KLHDC8A, TFEC/RHAG, TFEC/RHCE, TFEC/RNF182, TFEC/SPTA1, TFEC/THEM5, TFEC/TLCD4, TFEC/TMCC2, TFEC/TSPAN5, TFEC/TSPO2, THEM5/CARD17, THEM5/IFIT1B, TLCD4/ANKRD22, TLCD4/CARD17, TLCD4/GBP5, TLCD4/GLRX5, TLCD4/GYP A, TLCD4/IFIT1B, TLCD4/ITLN1, TLCD4/KLHDC8A, TLCD4/P2RY14, TLCD4/RHCE, TLCD4/RNF182, TLCD4/SPTA1, TLCD4/THEM5, TLCD4/TSPAN5, TMCC2/ANKRD22, TMCC2/CA1, TMCC2/CARD17, TMCC2/DYRK3, TMCC2/FAM83A, TMCC2/GBP5, TMCC2/GLRX5, TMCC2/GYP A, TMCC2/IFIT1B, TMCC2/ITLN1, TMCC2/KLHDC8A, TMCC2/P2RY14, TMCC2/RHCE, TMCC2/RNF182, TMCC2/SPTA1, TMCC2/THEM5, TMCC2/TLCD4, TMCC2/TSPAN5, TSPAN5/CARD17, TSPAN5/GLRX5, TSPAN5/GYP A, TSPAN5/IFIT1B, TSPAN5/ITLN1, TSPAN5/P2RY14, TSPAN5/RHCE, TSPAN5/RNF182, TSPAN5/THEM5, TSPO2/ANKRD22, TSPO2/CA1, TSPO2/CARD17, TSPO2/CD274, TSPO2/DYRK3, TSPO2/FAM83A, TSPO2/GBP5, TSPO2/GLRX5, TSPO2/GYP A, TSPO2/IFIT1B, TSPO2/ITLN1, TSPO2/KLHDC8A, TSPO2/P2RY14, TSPO2/RHCE, TSPO2/RNF182, TSPO2/SPTA1, TSPO2/THEM5, TSPO2/TLCD4, TSPO2/TMCC2, and TSPO2/TSPAN5; wherein the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1,

SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1, ADAM23/GPR34, ADAM23/MAP7, ADAM23/PLCB1, ADAM23/SPRED1, ALOX15/GPR34, ALOX15/PLCB1, ALOX15/SPRED1, BAALC/GPR34, BAALC/PLCB1, BAALC/SPRED1, CACNA2D3/DYNC2H1, CACNA2D3/GPR34, CACNA2D3/PLCB1, CACNA2D3/SPRED1, CACNA2D3/ZNF600, GPR34/DYNC2H1, GPR34/GRAMD1C, GPR34/PLCB1, GPR34/TPRG1, GPR34/ZNF600, GPR82/DYNC2H1, GPR82/GPR34, GPR82/GRAMD1C, GPR82/PLCB1, GPR82/TPRG1, GPR82/ZNF600, GRAMD1C/DYNC2H1, GRAMD1C/PLCB1, GRAMD1C/ZNF600, HRK/DYNC2H1, HRK/GPR34, HRK/MAP7, HRK/PLCB1, HRK/SPRED1, HRK/ZNF600, IL5RA/DYNC2H1, IL5RA/GPR34, IL5RA/PLCB1, IL5RA/SPRED1, IL5RA/TRIM2, MAP7/BAALC, MAP7/CACNA2D3, MAP7/DYNC2H1, MAP7/GPR34, MAP7/GPR82, MAP7/GRAMD1C, MAP7/PLCB1, MAP7/SPRED1, MAP7/TPRG1, MAP7/ZNF600, PLCB1/DYNC2H1, PLCB1/TPRG1, PLCB1/ZNF600, PRSS33/GPR34, PRSS33/PLCB1, PRSS33/SPRED1, SDC2/DYNC2H1, SDC2/GPR34, SDC2/PLCB1, SDC2/ZNF600, SIGLEC8/DYNC2H1, SIGLEC8/GPR34, SIGLEC8/MAP7, SIGLEC8/PLCB1, SIGLEC8/SPRED1, SIGLEC8/TRIM2, SMPD3/DYNC2H1, SMPD3/GPR34, SMPD3/MAP7, SMPD3/PLCB1, SMPD3/SPRED1, SMPD3/TRIM2, SPRED1/DYNC2H1, SPRED1/GPR34, SPRED1/GPR82, SPRED1/GRAMD1C, SPRED1/PLCB1, SPRED1/SDC2, SPRED1/TPRG1, SPRED1/ZNF600, TRIM2/CACNA2D3, TRIM2/DYNC2H1, TRIM2/GPR34, TRIM2/GPR82, TRIM2/GRAMD1C, TRIM2/HRK, TRIM2/MAP7, TRIM2/PLCB1, TRIM2/SDC2, TRIM2/SPRED1, TRIM2/TPRG1, and TRIM2/ZNF600; wherein the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1, APOL1/BATF2, APOL1/CLEC4F, APOL1/EPSTI1, APOL1/EXOC3L1, APOL1/HES4, APOL1/IFITM3, APOL1/LY6E, APOL1/RSAD2, APOL1/SEPTIN4, APOL1/SERPING1, APOL1/TPPP3, BATF2/EXOC3L1, BATF2/HES4, CLEC4F/BATF2, CLEC4F/EXOC3L1, EPSTI1/BATF2, EPSTI1/CLEC4F, EPSTI1/EXOC3L1, EPSTI1/HES4, EPSTI1/IFITM3, EPSTI1/LY6E, EPSTI1/RSAD2, EPSTI1/SERPING1, EPSTI1/TPPP3, ETV7/APOL1, ETV7/BATF2, ETV7/CLEC4F, ETV7/EPSTI1, ETV7/EXOC3L1, ETV7/HES4, ETV7/IFITM3, ETV7/LAMP3, ETV7/LY6E, ETV7/PLEKHO1, ETV7/RSAD2, ETV7/SEPTIN4,

ETV7/SERPING1, ETV7/TPPP3, EXOC3L1/HES4, IFITM3/SERPING1, IFITM3/CLEC4F, IFITM3/TPPP3, IFITM3/LY6E, IFITM3/EXOC3L1, IFITM3/HES4, LAMP3/APOL1, LAMP3/BATF2, LAMP3/CLEC4F, LAMP3/EPSTI1, LAMP3/EXOC3L1, LAMP3/HES4, LAMP3/IFITM3, LAMP3/LY6E, LAMP3/RSAD2, LAMP3/SEPTIN4, LAMP3/SERPING1, LAMP3/TPPP3, LY6E/BATF2, LY6E/EXOC3L1, PLEKHO1/APOL1, PLEKHO1/BATF2, PLEKHO1/EPSTI1, PLEKHO1/EXOC3L1, PLEKHO1/IFITM3, PLEKHO1/LAMP3, PLEKHO1/RSAD2, PLEKHO1/SEPTIN4, PLEKHO1/SERPING1, RSAD2/BATF2, RSAD2/CLEC4F, RSAD2/EXOC3L1, RSAD2/HES4, RSAD2/IFITM3, RSAD2/LY6E, RSAD2/SERPING1, RSAD2/TPPP3, SEPTIN4/BATF2, SEPTIN4/CLEC4F, SEPTIN4/EPSTI1, SEPTIN4/EXOC3L1, SEPTIN4/HES4, SEPTIN4/IFITM3, SEPTIN4/LY6E, SEPTIN4/RSAD2, SEPTIN4/SERPING1, SEPTIN4/TPPP3, SERPING1/BATF2, SERPING1/CLEC4F, SERPING1/EXOC3L1, SERPING1/HES4, SERPING1/LY6E, SERPING1/TPPP3, TPPP3/BATF2, and TPPP3/EXOC3L1; and wherein the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL, CAV1/LGALS3BP, CAV1/OTOF, CDC45/LGALS3BP, CDC45/OTOF, CENPF/KCTD14, GPRC5D/OTOF, GTSE1/LGALS3BP, GTSE1/OTOF, IGF1/LGALS3BP, IGF1/OTOF, KCTD14/KLHL14, KCTD14/PDIA4, KCTD14/TSHR, KIF14/KCTD14, LGALS3BP/CENPF, LGALS3BP/GPRC5D, LGALS3BP/IFI27, LGALS3BP/IGLL5, LGALS3BP/KCTD14, LGALS3BP/KIF14, LGALS3BP/KIF15, LGALS3BP/KLHL14, LGALS3BP/MIR155HG, LGALS3BP/MIXL1, LGALS3BP/OTOF, LGALS3BP/PDIA4, LGALS3BP/PLAAT2, LGALS3BP/SDC1, LGALS3BP/SLC16A14, LGALS3BP/TSHR, OTOF/CENPF, OTOF/IFI27, OTOF/IGLL5, OTOF/KCTD14, OTOF/KIF14, OTOF/KIF15, OTOF/KLHL14, OTOF/MIR155HG, OTOF/MIXL1, OTOF/PDIA4, OTOF/PLAAT2, OTOF/SDC1, OTOF/SLC16A14, OTOF/TSHR, PLAAT2/KCTD14, TNFRSF17/LGALS3BP, and TNFRSF17/OTOF.

[0021] In an embodiment, the reference gene signature represents a standard level of expression of the genes comprised therein and a difference between a sample endotype signature pair and a reference endotype signature pair indicates that the subject has the sepsis mechanistic endotype corresponding to that signature pair.

[0022] In an embodiment, the sample gene signature and the reference gene signature comprise the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, and the ADA endotype signature pair.

[0023] In an embodiment, the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, and MLLT1/KLF14. In another embodiment, the INF endotype signature pair is selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, and SPTA1/FECH. In a further embodiment, the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, and CACNA2D3/SPRED1. In another embodiment, the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, and LAMP3/SERPING1. In an embodiment, the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, and LGALS3BP/MIXL1.

[0024] The present disclosure also includes a method for predicting severity of sepsis in a subject, wherein the severity of the sepsis is selected from high severity sepsis, intermediate severity sepsis and low severity sepsis, the method comprising: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5, and low severity sepsis means a SOFA score of less than 2; and wherein the plurality of genes is selected from

the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19.

[0025] In an embodiment, the plurality of genes comprises CCL4L2, GPR84, HRK, MMP8, GGT5, and RASGRF1. In another embodiment, the plurality of genes is CCL4L2, GPR84, HRK, MMP8, GGT5, and RASGRF1.

[0026] In an embodiment, determining the level of expression comprises detecting nucleic acids encoded by each of the plurality of genes. In another embodiment, determining the level of expression comprises one or more of a polymerase chain reaction (PCR) amplification method, a non-PCR based amplification method, reverse transcriptase-(RT) PCR, Q-beta replicase amplification, ligase chain reaction, signal amplification (Ampliprobe), light cycling, differential display, Northern analysis, hybridization, microarray analysis, DNA sequencing, RNA sequencing (RNA-Seq), MassArray analysis and MALDI-TOF mass spectrometry. In a further embodiment, determining the level of expression comprises a polymerase chain reaction (PCR) amplification method. In another embodiment, determining the level of expression comprises RNA sequencing (RNA-Seq).

[0027] In an embodiment, the biological sample comprises sputum, blood, nasal brushings, throat swabs, urine, amniotic fluid, plasma, serum, saliva, semen, bone marrow, tissue or fine needle

biopsy samples, stool, bronchoalveolar lavage fluid, cerebrospinal fluid, peritoneal fluid, pleural fluid, skin, or cells therefrom. In another embodiment, the biological sample comprises blood. In an embodiment, the biological sample has been obtained from the subject prior to admission in an intensive care unit. In another embodiment, the biological sample has been obtained from the subject at first clinical presentation. In a further embodiment, the biological sample has been obtained from the subject within the first day after entry into an intensive care unit.

[0028] The present disclosure also includes a use of one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype, for treatment of sepsis in a subject classified as having the sepsis mechanistic endotype by a method for classifying a subject into a sepsis mechanistic endotype of the present disclosure.

[0029] The present disclosure also includes one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype for use to treat sepsis in a subject classified as having the sepsis mechanistic endotype by a method for classifying a subject into a sepsis mechanistic endotype of the present disclosure.

[0030] The present disclosure also includes a use of an effective amount of one or more antibiotics for treatment of sepsis in a subject predicted as having high or intermediate severity sepsis by a method comprising: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, and intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5; and wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK,

METTTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19.

[0031] The present disclosure also includes one or more antibiotics for use to treat sepsis in a subject predicted as having high or intermediate severity sepsis by a method for predicting severity of sepsis comprising: (i) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (ii) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, and intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5; and wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19.

[0032] In an embodiment, the one or more antibiotics is one or a combination of a glycopeptide, a cephalosporin, a beta-lactam, a beta-lactamase inhibitor, a carbapenem, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide and a monobactam.

[0033] The present disclosure also includes a kit: (a) for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the kit comprising gene specific reagents, each of the gene specific reagents capable of detecting an expression product of: (i) a respective one of a plurality of genes or complement thereof in an NPS endotype sub-signature, an INF endotype sub-signature, an IHD endotype sub-signature, an IFN endotype sub-signature, an ADA endotype sub-signature or combinations thereof, wherein the NPS endotype sub-signature, the INF endotype sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, the ADA endotype sub-signature or combinations thereof are as described herein; or (ii) a respective one of a plurality of genes or complement thereof in an NPS endotype signature pair, an INF endotype signature pair, an IHD endotype signature pair, an IFN endotype signature pair, an ADA endotype signature pair or combinations thereof, wherein the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, the ADA endotype signature pair or combinations thereof are as described herein; or (b) for predicting severity of sepsis in a subject, wherein the severity of the sepsis is selected from high severity sepsis, intermediate severity sepsis and low severity sepsis, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5, and low severity sepsis means a SOFA score of less than 2, the kit comprising gene specific reagents, each of the gene specific reagents capable of detecting an expression product of a respective one of a plurality of genes as described herein or complement thereof; and optionally instructions for use.

[0034] The present disclosure also includes a method for identifying a candidate agent for the treatment of sepsis in a subject classified as having a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising: (a) contacting a cell having the sepsis endotype with a test agent, (b) determining the level of expression for each of a plurality of genes in the cell to provide an expression signature; (c) comparing the expression signature with a reference signature, wherein the reference

signature represents the level of expression of the plurality of genes in a normal cell; and (d) selecting the test agent as a candidate agent for treatment of the sepsis when the expression signature substantially corresponds with the reference signature, wherein the expression signature and reference signature comprise: (a) an NPS endotype sub-signature for an NPS endotype cell, an INF endotype sub-signature for an INF endotype cell, an IHD endotype sub-signature for an IHD endotype cell, an IFN endotype sub-signature for an IFN endotype cell and an ADA endotype sub-signature for an ADA endotype cell, wherein the NPS endotype sub-signature, the INF endotype sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, the ADA endotype sub-signature or combinations thereof are as described herein; or (b) an NPS endotype signature pair for an NPS endotype cell, an INF endotype signature pair for an INF endotype cell, an IHD endotype signature pair for an IHD endotype cell, an IFN endotype signature pair for an IFN endotype cell, and an ADA endotype signature pair for an ADA endotype cell, wherein the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, the ADA endotype signature pair or combinations thereof are as described herein.

[0035] In an embodiment is provided a method of detecting a sepsis mechanistic endotype, using endotype-specific gene signatures for the NPS, INF, IHD, IFN and ADA endotypes, in a biological sample obtained from a subject suspected of having sepsis, at risk of developing severe sepsis, at risk of organ failure, or having endotoxin tolerance, the method comprising detecting a level of expression, in a biological sample obtained from the subject, for each of a plurality of Endotoxin Tolerance Signature genes to provide a sample gene signature, wherein plurality of genes is selected from the group consisting of **NPS signature:** AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, XCR1; **INF signature:** BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE,

RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, YPEL4; **IHD signature:** ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, TRIM2; **IFN signature:** ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, LAMP3; **ADA signature:** CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, TTC21A, wherein an Endotype Signature gene signature is detected when the sample gene signature is different from a reference gene signature, wherein the reference gene signature represents a standard level of expression of each of the plurality of genes.

[0036] In another embodiment is provided a method of detecting a sepsis mechanistic endotype, using endotype-specific gene signatures for the NPS, INF, IHD, IFN and ADA endotypes, in a biological sample obtained from a subject suspected of having sepsis, at risk of developing severe sepsis, at risk of organ failure, or having endotoxin tolerance, the method comprising detecting a level of expression, in a biological sample obtained from the subject, for each of a plurality of Endotoxin Tolerance Signature genes to provide a sample gene

signature, wherein plurality of genes is selected from the group consisting of **NPS-selective:** AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19; **INF-selective:** BNIP3L, CA1, FAM83A, FECH, GLRX5, GYPA, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, **IHD-selective:** ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600; **IFN-selective:** ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC; **ADA-selective:** CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1.

[0037] In an embodiment, the difference between the sample gene signature and the reference gene signature is defined by a difference in expression of at least two of the plurality of genes in an expression change direction, at least 5 of the plurality of genes in an expression change direction, at least 10 of the plurality of genes in an expression change direction, at least 15 of the plurality of genes in an expression change direction, at least 20 of the plurality of genes in an expression change direction, at least 25 of the plurality of genes in an expression change direction, at least 30 of the plurality of genes in an expression change direction, or at least 31 of the plurality of genes in an expression change direction.

[0038] In another embodiment is provided a method of detecting a sepsis mechanistic endotype, using endotype-specific gene signatures for the NPS, INF, IHD, IFN and ADA endotypes, in a biological sample obtained from a subject suspected of having sepsis, at risk of developing severe sepsis, at risk of organ failure, or having endotoxin tolerance, the method comprising detecting a level of expression, in a biological sample obtained from the subject, for each of a plurality of Endotoxin Tolerance Signature genes to provide a sample gene signature, wherein plurality of genes is selected from the group consisting of two genes, and wherein the pair of genes are selected from the pairs comprising **NPS signature pairs:** GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/ PFKFB2, MLLT1/KLF14. ADAMTS3/PCOLCE2; ADAMTS3/ZDHHC19; ADAMTS3/SLC51A; ADAMTS3/HPGD; ADAMTS3/SEMA6B; ADAMTS3/EFNA1; ADAMTS3/AGFG1;

ADAMTS3/NSUN7; ADAMTS3/TNFAIP8L3; ADAMTS3/KREMEN1;
 ADAMTS3/ORM2; ADAMTS3/MIR646HG; ADAMTS3/KLF14; AGFG1/NSUN7;
 AGFG1/TNFAIP8L3; AGFG1/KREMEN1; AGFG1/ORM2; AGFG1/MIR646HG;
 AGFG1/KLF14; ANXA3/GPR84; ANXA3/OLAH; ANXA3/ADAMTS3;
 ANXA3/PCOLCE2; ANXA3/ZDHHC19; ANXA3/SLC51A; ANXA3/HPGD;
 ANXA3/SEMA6B; ANXA3/EFNA1; ANXA3/AGFG1; ANXA3/NSUN7;
 ANXA3/TNFAIP8L3; ANXA3/KREMEN1; ANXA3/ORM2; ANXA3/MIR646HG;
 ANXA3/KLF14; ARG1/PFKFB2; ARG1/MLLT1; ARG1/ANXA3; ARG1/GPR84;
 ARG1/OLAH; ARG1/ADAMTS3; ARG1/PCOLCE2; ARG1/ZDHHC19; ARG1/SLC51A;
 ARG1/HPGD; ARG1/SEMA6B; ARG1/EFNA1; ARG1/AGFG1; ARG1/NSUN7;
 ARG1/TNFAIP8L3; ARG1/KREMEN1; ARG1/ORM2; ARG1/MIR646HG; ARG1/KLF14;
 ATP9A/EPB41L4B; ATP9A/IL1R1; ATP9A/GADD45A; ATP9A/ARG1;
 ATP9A/PFKFB2; ATP9A/MLLT1; ATP9A/ANXA3; ATP9A/GPR84; ATP9A/OLAH;
 ATP9A/ADAMTS3; ATP9A/PCOLCE2; ATP9A/ZDHHC19; ATP9A/SLC51A;
 ATP9A/HPGD; ATP9A/SEMA6B; ATP9A/EFNA1; ATP9A/AGFG1; ATP9A/NSUN7;
 ATP9A/TNFAIP8L3; ATP9A/KREMEN1; ATP9A/ORM2; ATP9A/MIR646HG;
 ATP9A/KLF14; EFNA1/AGFG1; EFNA1/NSUN7; EFNA1/TNFAIP8L3;
 EFNA1/KREMEN1; EFNA1/ORM2; EFNA1/MIR646HG; EFNA1/KLF14;
 EPB41L4B/IL1R1; EPB41L4B/GADD45A; EPB41L4B/ARG1; EPB41L4B/PFKFB2;
 EPB41L4B/MLLT1; EPB41L4B/ANXA3; EPB41L4B/GPR84; EPB41L4B/OLAH;
 EPB41L4B/ADAMTS3; EPB41L4B/PCOLCE2; EPB41L4B/ZDHHC19;
 EPB41L4B/SLC51A; EPB41L4B/HPGD; EPB41L4B/SEMA6B; EPB41L4B/EFNA1;
 EPB41L4B/AGFG1; EPB41L4B/NSUN7; EPB41L4B/TNFAIP8L3;
 EPB41L4B/KREMEN1; EPB41L4B/MIR646HG; EPB41L4B/KLF14; GADD45A/ARG1;
 GADD45A/PFKFB2; GADD45A/MLLT1; GADD45A/ANXA3; GADD45A/GPR84;
 GADD45A/OLAH; GADD45A/ADAMTS3; GADD45A/PCOLCE2;
 GADD45A/ZDHHC19; GADD45A/SLC51A; GADD45A/HPGD; GADD45A/SEMA6B;
 GADD45A/EFNA1; GADD45A/AGFG1; GADD45A/NSUN7; GADD45A/TNFAIP8L3;
 GADD45A/KREMEN1; GADD45A/ORM2; GADD45A/MIR646HG; GADD45A/KLF14;
 GPR84/OLAH; GPR84/ADAMTS3; GPR84/PCOLCE2; GPR84/ZDHHC19;
 GPR84/SLC51A; GPR84/HPGD; GPR84/SEMA6B; GPR84/EFNA1; GPR84/AGFG1;
 GPR84/NSUN7; GPR84/TNFAIP8L3; GPR84/KREMEN1; GPR84/ORM2;
 GPR84/MIR646HG; GPR84/KLF14; HPGD/SEMA6B; HPGD/EFNA1; HPGD/AGFG1;

HPGD/NSUN7; HPGD/TNFAIP8L3; HPGD/KREMEN1; HPGD/ORM2;
 HPGD/MIR646HG; HPGD/KLF14; IL1R1/GADD45A; IL1R1/ARG1; IL1R1/PFKFB2;
 IL1R1/MLLT1; IL1R1/ANXA3; IL1R1/GPR84; IL1R1/OLAH; IL1R1/ADAMTS3;
 IL1R1/PCOLCE2; IL1R1/ZDHHC19; IL1R1/SLC51A; IL1R1/HPGD; IL1R1/SEMA6B;
 IL1R1/EFNA1; IL1R1/AGFG1; IL1R1/NSUN7; IL1R1/TNFAIP8L3; IL1R1/KREMEN1;
 IL1R1/ORM2; IL1R1/MIR646HG; IL1R1/KLF14; KREMEN1/ORM2;
 KREMEN1/MIR646HG; KREMEN1/KLF14; MIR646HG/KLF14; MLLT1/ANXA3;
 MLLT1/GPR84; MLLT1/OLAH; MLLT1/ADAMTS3; MLLT1/PCOLCE2;
 MLLT1/ZDHHC19; MLLT1/SLC51A; MLLT1/HPGD; MLLT1/SEMA6B;
 MLLT1/EFNA1; MLLT1/AGFG1; MLLT1/SUN7; MLLT1/TNFAIP8L3;
 MLLT1/KREMEN1; MLLT1/ORM2; MLLT1/MIR646HG; MLLT1/KLF14;
 NSUN7/TNFAIP8L3; NSUN7/KREMEN1; NSUN7/ORM2; NSUN7/MIR646HG;
 NSUN7/KLF14; OLAH/ADAMTS3; OLAH/PCOLCE2; OLAH/ZDHHC19;
 OLAH/SLC51A; OLAH/HPGD; OLAH/SEMA6B; OLAH/EFNA1; OLAH/AGFG1;
 OLAH/NSUN7; OLAH/TNFAIP8L3; OLAH/KREMEN1; OLAH/ORM2;
 OLAH/MIR646HG; OLAH/KLF14; ORM2/MIR646HG; ORM2/KLF14;
 PCOLCE2/ZDHHC19; PCOLCE2/SLC51A; PCOLCE2/HPGD; PCOLCE2/SEMA6B;
 PCOLCE2/EFNA1; PCOLCE2/AGFG1; PCOLCE2/NSUN7; PCOLCE2/TNFAIP8L3;
 PCOLCE2/KREMEN1; PCOLCE2/ORM2; PCOLCE2/MIR646HG; PCOLCE2/KLF14;
 PFKFB2/MLLT1; PFKFB2/ANXA3; PFKFB2/GPR84; PFKFB2/OLAH;
 PFKFB2/ADAMTS3; PFKFB2/PCOLCE2; PFKFB2/ZDHHC19; PFKFB2/SLC51A;
 PFKFB2/HPGD; PFKFB2/SEMA6B; PFKFB2/EFNA1; PFKFB2/AGFG1;
 PFKFB2/NSUN7; PFKFB2/TNFAIP8L3; PFKFB2/KREMEN1; PFKFB2/ORM2;
 PFKFB2/MIR646HG; PFKFB2/KLF14; SEMA6B/EFNA1; SEMA6B/AGFG1;
 SEMA6B/NSUN7; SEMA6B/TNFAIP8L3; SEMA6B/KREMEN1; SEMA6B/ORM2;
 SEMA6B/MIR646HG; SEMA6B/KLF14; SLC51A/HPGD; SLC51A/SEMA6B;
 SLC51A/EFNA1; SLC51A/AGFG1; SLC51A/NSUN7; SLC51A/TNFAIP8L3;
 SLC51A/KREMEN1; SLC51A/ORM2; SLC51A/MIR646HG; SLC51A/KLF14;
 TNFAIP8L3/KREMEN1; TNFAIP8L3/ORM2; TNFAIP8L3/MIR646HG;
 TNFAIP8L3/KLF14; ZDHHC19/SLC51A; ZDHHC19/HPGD; ZDHHC19/SEMA6B;
 ZDHHC19/EFNA1; ZDHHC19/AGFG1; ZDHHC19/NSUN7; ZDHHC19/TNFAIP8L3;
 ZDHHC19/KREMEN1; ZDHHC19/ORM2; ZDHHC19/MIR646HG; ZDHHC19/KLF14;
INF signature pairs: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH,

FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, SPTA1/FECH, ANKRD22/GLRX5; ANKRD22/GYP A; ANKRD22/IFIT1B; ANKRD22/ITLN1; ANKRD22/KLHDC8A; ANKRD22/RHCE; ANKRD22/RNF182; ANKRD22/SPTA1; ANKRD22/THEM5; ANKRD22/TSPAN5; APOL4/BNIP3L; APOL4/CA1; APOL4/DYRK3; APOL4/FAM83A; APOL4/GLRX5; APOL4/GYP A; APOL4/IFIT1B; APOL4/ITLN1; APOL4/KLHDC8A; APOL4/RHAG; APOL4/RHCE; APOL4/RIOK3; APOL4/RNF182; APOL4/SPTA1; APOL4/THEM5; APOL4/TLCD4; APOL4/TMCC2; APOL4/TSPAN5; APOL4/TSPO2; BNIP3L/ANKRD22; BNIP3L/CA1; BNIP3L/CARD17; BNIP3L/CD274; BNIP3L/DYRK3; BNIP3L/FAM83A; BNIP3L/GBP5; BNIP3L/GLRX5; BNIP3L/GYP A; BNIP3L/IFIT1B; BNIP3L/ITLN1; BNIP3L/KLHDC8A; BNIP3L/P2RY14; BNIP3L/RHAG; BNIP3L/RHCE; BNIP3L/RNF182; BNIP3L/SPTA1; BNIP3L/TFEC; BNIP3L/THEM5; BNIP3L/TLCD4; BNIP3L/TMCC2; BNIP3L/TSPAN5; BNIP3L/TSPO2; CA1/ANKRD22; CA1/CARD17; CA1/DYRK3; CA1/FAM83A; CA1/GBP5; CA1/GLRX5; CA1/GYP A; CA1/IFIT1B; CA1/ITLN1; CA1/KLHDC8A; CA1/P2RY14; CA1/RHCE; CA1/RNF182; CA1/SPTA1; CA1/THEM5; CA1/TLCD4; CA1/TSPAN5; CD274/CA1; CD274/DYRK3; CD274/FAM83A; CD274/GLRX5; CD274/GYP A; CD274/IFIT1B; CD274/ITLN1; CD274/KLHDC8A; CD274/RHCE; CD274/RNF182; CD274/SPTA1; CD274/THEM5; CD274/TLCD4; CD274/TMCC2; CD274/TSPAN5; DYRK3/ANKRD22; DYRK3/CARD17; DYRK3/FAM83A; DYRK3/GBP5; DYRK3/GLRX5; DYRK3/GYP A; DYRK3/IFIT1B; DYRK3/ITLN1; DYRK3/KLHDC8A; DYRK3/P2RY14; DYRK3/RHCE; DYRK3/RNF182; DYRK3/SPTA1; DYRK3/THEM5; DYRK3/TLCD4; DYRK3/TSPAN5; FAM83A/ANKRD22; FAM83A/CARD17; FAM83A/GBP5; FAM83A/GLRX5; FAM83A/GYP A; FAM83A/IFIT1B; FAM83A/ITLN1; FAM83A/KLHDC8A; FAM83A/P2RY14; FAM83A/RHCE; FAM83A/RNF182; FAM83A/SPTA1; FAM83A/THEM5; FAM83A/TLCD4; FAM83A/TSPAN5; FECH/ANKRD22; FECH/APOL4; FECH/BNIP3L; FECH/CA1; FECH/CARD17; FECH/CD274; FECH/DYRK3; FECH/FAM83A; FECH/GBP5; FECH/GLRX5; FECH/GYP A; FECH/IFIT1B; FECH/ITLN1; FECH/KLHDC8A; FECH/P2RY14; FECH/RHAG; FECH/RHCE; FECH/RIOK3; FECH/RNF182; FECH/SPTA1; FECH/TFEC; FECH/THEM5; FECH/TLCD4; FECH/TMCC2; FECH/TSPAN5; FECH/TSPO2; GBP5/GLRX5; GBP5/GYP A; GBP5/IFIT1B; GBP5/ITLN1; GBP5/KLHDC8A; GBP5/RHCE; GBP5/RNF182; GBP5/SPTA1; GBP5/THEM5; GBP5/TSPAN5;

GLRX5/CARD17; GLRX5/IFIT1B; GLRX5/RHCE; GLRX5/THEM5; GYP A/CARD17;
 GYP A/GLRX5; GYP A/IFIT1B; GYP A/ITLN1; GYP A/P2RY14; GYP A/RHCE;
 GYP A/RNF182; GYP A/THEM5; IFIT1B/CARD17; ITLN1/CARD17; ITLN1/GLRX5;
 ITLN1/IFIT1B; ITLN1/RHCE; ITLN1/RNF182; ITLN1/THEM5; KLHDC8A/CARD17;
 KLHDC8A/GLRX5; KLHDC8A/GYP A; KLHDC8A/IFIT1B; KLHDC8A/ITLN1;
 KLHDC8A/P2RY14; KLHDC8A/RHCE; KLHDC8A/RNF182; KLHDC8A/SPTA1;
 KLHDC8A/THEM5; KLHDC8A/TSPAN5; P2RY14/GLRX5; P2RY14/IFIT1B;
 P2RY14/ITLN1; P2RY14/RHCE; P2RY14/RNF182; P2RY14/THEM5; RHAG/ANKRD22;
 RHAG/CA1; RHAG/CARD17; RHAG/CD274; RHAG/DYRK3; RHAG/FAM83A;
 RHAG/GBP5; RHAG/GLRX5; RHAG/GYP A; RHAG/IFIT1B; RHAG/ITLN1;
 RHAG/KLHDC8A; RHAG/P2RY14; RHAG/RHCE; RHAG/RNF182; RHAG/SPTA1;
 RHAG/THEM5; RHAG/TLCD4; RHAG/TMCC2; RHAG/TSPAN5; RHAG/TSPO2;
 RHCE/CARD17; RHCE/IFIT1B; RHCE/THEM5; RIOK3/ANKRD22; RIOK3/BNIP3L;
 RIOK3/CA1; RIOK3/CARD17; RIOK3/CD274; RIOK3/DYRK3; RIOK3/FAM83A;
 RIOK3/GBP5; RIOK3/GLRX5; RIOK3/GYP A; RIOK3/IFIT1B; RIOK3/ITLN1;
 RIOK3/KLHDC8A; RIOK3/P2RY14; RIOK3/RHAG; RIOK3/RHCE; RIOK3/RNF182;
 RIOK3/SPTA1; RIOK3/TFEC; RIOK3/THEM5; RIOK3/TLCD4; RIOK3/TMCC2;
 RIOK3/TSPAN5; RIOK3/TSPO2; RNF182/CARD17; RNF182/GLRX5; RNF182/IFIT1B;
 RNF182/RHCE; RNF182/THEM5; SPTA1/CARD17; SPTA1/GLRX5; SPTA1/GYP A;
 SPTA1/IFIT1B; SPTA1/ITLN1; SPTA1/P2RY14; SPTA1/RHCE; SPTA1/RNF182;
 SPTA1/THEM5; SPTA1/TSPAN5; TFEC/CA1; TFEC/DYRK3; TFEC/FAM83A;
 TFEC/GLRX5; TFEC/GYP A; TFEC/IFIT1B; TFEC/ITLN1; TFEC/KLHDC8A;
 TFEC/RHAG; TFEC/RHCE; TFEC/RNF182; TFEC/SPTA1; TFEC/THEM5;
 TFEC/TLCD4; TFEC/TMCC2; TFEC/TSPAN5; TFEC/TSPO2; THEM5/CARD17;
 THEM5/IFIT1B; TLCD4/ANKRD22; TLCD4/CARD17; TLCD4/GBP5; TLCD4/GLRX5;
 TLCD4/GYP A; TLCD4/IFIT1B; TLCD4/ITLN1; TLCD4/KLHDC8A; TLCD4/P2RY14;
 TLCD4/RHCE; TLCD4/RNF182; TLCD4/SPTA1; TLCD4/THEM5; TLCD4/TSPAN5;
 TMCC2/ABCA6; TMCC2/ANKRD22; TMCC2/CA1; TMCC2/CARD17;
 TMCC2/DYRK3; TMCC2/FAM83A; TMCC2/GBP5; TMCC2/GLRX5; TMCC2/GYP A;
 TMCC2/IFIT1B; TMCC2/ITLN1; TMCC2/KLHDC8A; TMCC2/P2RY14; TMCC2/RHCE;
 TMCC2/RNF182; TMCC2/SPTA1; TMCC2/THEM5; TMCC2/TLCD4; TMCC2/TSPAN5;
 TSPAN5/CARD17; TSPAN5/GLRX5; TSPAN5/GYP A; TSPAN5/IFIT1B;
 TSPAN5/ITLN1; TSPAN5/P2RY14; TSPAN5/RHCE; TSPAN5/RNF182;

TSPAN5/THEM5; TSP02/ANKRD22; TSP02/CA1; TSP02/CARD17; TSP02/CD274; TSP02/DYRK3; TSP02/FAM83A; TSP02/GBP5; TSP02/GLRX5; TSP02/GYP A; TSP02/IFIT1B; TSP02/ITLN1; TSP02/KLHDC8A; TSP02/P2RY14; TSP02/RHCE; TSP02/RNF182; TSP02/SPTA1; TSP02/THEM5; TSP02/TLCD4; TSP02/TMCC2; TSP02/TSPAN5. **IHD signature pairs:** MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1, ADAM23/GPR34; ADAM23/MAP7; ADAM23/PLCB1; ADAM23/SPRED1; ALOX15/GPR34; ALOX15/PLCB1; ALOX15/SPRED1; BAALC/GPR34; BAALC/PLCB1; BAALC/SPRED1; CACNA2D3/DYNC2H1; CACNA2D3/GPR34; CACNA2D3/PLCB1; CACNA2D3/SPRED1; CACNA2D3/ZNF600; GPR34/DYNC2H1; GPR34/GRAMD1C; GPR34/PLCB1; GPR34/PRG1; GPR34/ZNF600; GPR82/DYNC2H1; GPR82/GPR34; GPR82/GRAMD1C; GPR82/PLCB1; GPR82/TPRG1; GPR82/ZNF600; GRAMD1C/DYNC2H1; GRAMD1C/PLCB1; GRAMD1C/ZNF600; HRK/DYNC2H1; HRK/GPR34; HRK/MAP7; HRK/PLCB1; HRK/SPRED1; HRK/ZNF600; IL5RA/DYNC2H1; IL5RA/GPR34; IL5RA/PLCB1; IL5RA/SPRED1; IL5RA/TRIM2; MAP7/BAALC; MAP7/CACNA2D3; MAP7/DYNC2H1; MAP7/GPR34; MAP7/GPR82; MAP7/GRAMD1C; MAP7/PLCB1; MAP7/SPRED1; MAP7/TPRG1; MAP7/ZNF600; PLCB1/DYNC2H1; PLCB1/TPRG1; PLCB1/ZNF600; PRSS33/GPR34; PRSS33/PLCB1; PRSS33/SPRED1; SDC2/DYNC2H1; SDC2/GPR34; SDC2/PLCB1; SDC2/ZNF600; SIGLEC8/DYNC2H1; SIGLEC8/GPR34; SIGLEC8/MAP7; SIGLEC8/PLCB1; SIGLEC8/SPRED1; SIGLEC8/TRIM2; SMPD3/DYNC2H1; SMPD3/GPR34; SMPD3/MAP7; SMPD3/PLCB1; SMPD3/SPRED1; SMPD3/TRIM2; SPRED1/DYNC2H1; SPRED1/GPR34; SPRED1/GPR82; SPRED1/GRAMD1C; SPRED1/PLCB1; SPRED1/SDC2; SPRED1/TPRG1; SPRED1/ZNF600; TRIM2/CACNA2D3; TRIM2/DYNC2H1; TRIM2/GPR34; TRIM2/GPR82; TRIM2/GRAMD1C; TRIM2/HRK; TRIM2/MAP7; TRIM2/PLCB1; TRIM2/SDC2; TRIM2/SPRED1; TRIM2/TPRG1; TRIM2/ZNF600; **IFN signature pairs:** ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, ETV7/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1, APOL1/BATF2; APOL1/CLEC4F; APOL1/EPSTI1; APOL1/EXOC3L1; APOL1/HES4; APOL1/IFITM3; APOL1/LY6E; APOL1/RSAD2;

APOL1/SEPTIN4; APOL1/SERPING1; APOL1/TPPP3; BATF2/EXOC3L1;
 BATF2/HES4; CLEC4F/BATF2; CLEC4F/EXOC3L1; EPSTI1/BATF2; EPSTI1/CLEC4F;
 EPSTI1/EXOC3L1; EPSTI1/HES4; EPSTI1/IFITM3; EPSTI1/LY6E; EPSTI1/RSAD2;
 EPSTI1/SERPING1; EPSTI1/TPPP3; ETV7/APOL1; ETV7/BATF2; ETV7/CLEC4F;
 ETV7/EPSTI1; ETV7/EXOC3L1; ETV7/HES4; ETV7/IFITM3; ETV7/LAMP3;
 ETV7/LY6E; ETV7/PLEKHO1; ETV7/RSAD2; ETV7/SEPTIN4; ETV7/SERPING1;
 ETV7/TPPP3; EXOC3L1/HES4; LAMP3/APOL1; LAMP3/BATF2; LAMP3/CLEC4F;
 LAMP3/EPSTI1; LAMP3/EXOC3L1; LAMP3/HES4; LAMP3/IFITM3; LAMP3/LY6E;
 LAMP3/RSAD2; LAMP3/SEPTIN4; LAMP3/SERPING1; LAMP3/TPPP3; LY6E/BATF2;
 LY6E/EXOC3L1; PLEKHO1/APOL1; PLEKHO1/BATF2; PLEKHO1/EPSTI1;
 PLEKHO1/EXOC3L1; PLEKHO1/IFITM3; PLEKHO1/LAMP3; PLEKHO1/RSAD2;
 PLEKHO1/SEPTIN4; PLEKHO1/SERPING1; RSAD2/BATF2; RSAD2/CLEC4F;
 RSAD2/EXOC3L1; RSAD2/HES4; RSAD2/IFITM3; RSAD2/LY6E; RSAD2/SERPING1;
 RSAD2/TPPP3; SEPTIN4/BATF2; SEPTIN4/CLEC4F; SEPTIN4/EPSTI1;
 SEPTIN4/EXOC3L1; SEPTIN4/HES4; SEPTIN4/IFITM3; SEPTIN4/LGALS3BP;
 SEPTIN4/LY6E; SEPTIN4/OTOF; SEPTIN4/RSAD2; SEPTIN4/SERPING1;
 SEPTIN4/TPPP3; SERPING1/BATF2; SERPING1/CLEC4F; SERPING1/EXOC3L1;
 SERPING1/HES4; SERPING1/LY6E; SERPING1/TPPP3; TPPP3/BATF2;
 TPPP3/EXOC3L1; **ADA signature pairs:** LGALS3BP/OTOF, LGALS3BP/IFI27,
 LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14,
 LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27,
 IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5,
 LGALS3BP/MIXL, CAV1/LGALS3BP, CAV1/OTOF, CDC45/LGALS3BP;
 CDC45/OTOF; CENPF/KCTD14; GPRC5D/OTOF; GTSE1/LGALS3BP; GTSE1/OTOF;
 IGF1/LGALS3BP; IGF1/OTOF; KCTD14/KLHL14; KCTD14/PDIA4; KCTD14/TSHR;
 KIF14/KCTD14; LGALS3BP/CENPF; LGALS3BP/GPRC5D; LGALS3BP/IFI27;
 LGALS3BP/IGLL5; LGALS3BP/KCTD14; LGALS3BP/KIF14; LGALS3BP/KIF15;
 LGALS3BP/KLHL14; LGALS3BP/MIR155HG; LGALS3BP/MIXL1; LGALS3BP/OTOF;
 LGALS3BP/PDIA4; LGALS3BP/PLAAT2; LGALS3BP/SDC1; LGALS3BP/SLC16A14;
 LGALS3BP/TSHR; OTOF/CENPF; OTOF/IFI27; OTOF/IGLL5; OTOF/KCTD14;
 OTOF/KIF14; OTOF/KIF15; OTOF/KLHL14; OTOF/MIR155HG; OTOF/MIXL1;
 OTOF/PDIA4; OTOF/PLAAT2; OTOF/SDC1; OTOF/SLC16A14; OTOF/TSHR;
 PLAAT2/KCTD14; TNFRSF17/LGALS3BP; TNFRSF17/OTOF; or wherein the preferred

pairs may comprise **NPS signature pairs:** GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, MLLT1/KLF14. **INF signature pairs:** FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, SPTA1/FECH. **IHD signature pairs:** MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1. **IFN signature pairs:** ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, ETV7/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1. **ADA signature pairs:** LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL1.

[0039] In another embodiment is provided a method of detecting a sepsis mechanistic severity gene signature in a biological sample obtained from a subject suspected of having sepsis, at risk of developing severe sepsis, at risk of organ failure, or having endotoxin tolerance, the method comprising detecting a level of expression, in a biological sample obtained from the subject, for each of a plurality of Endotoxin Tolerance Signature genes to provide a sample gene signature, wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYP A, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B,

MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, ZDHHC19, wherein the severity gene signature is detected when the sample gene signature is different from a reference gene signature, wherein the reference gene signature represents a standard level of expression of each of the plurality of genes.

[0040] In an embodiment, the difference between the sample gene signature and the reference gene signature is defined by a difference in expression of at least two of the plurality of genes in an expression change direction, at least 5 of the plurality of genes in an expression change direction, at least 10 of the plurality of genes in an expression change direction, at least 15 of the plurality of genes in an expression change direction, at least 20 of the plurality of genes in an expression change direction, at least 25 of the plurality of genes in an expression change direction, at least 30 of the plurality of genes in an expression change direction, or at least 31 of the plurality of genes in an expression change direction.

[0041] In another embodiment is provided a method of detecting a sepsis mechanistic severity gene signature in a biological sample obtained from a subject suspected of having sepsis, at risk of developing severe sepsis, at risk of organ failure, or having endotoxin tolerance, the method comprising detecting a level of expression, in a biological sample obtained from the subject, for each of a plurality of Endotoxin Tolerance Signature genes to provide a sample gene signature, wherein plurality of genes is selected from the group consisting of ADAMTS2, RETN, MMP8, G0S2, CYP19A1, OLAH, SLC6A19, TNFAIP8L3.

[0042] In another embodiment is provided a method of detecting a sepsis mechanistic severity gene signature in a biological sample obtained from a subject suspected of having sepsis, at risk of developing severe sepsis, at risk of organ failure, or having endotoxin tolerance, the method comprising detecting a level of expression, in a biological sample obtained from the subject, for each of a plurality of Endotoxin Tolerance Signature genes to provide a sample gene signature, wherein plurality of genes is selected from the group consisting of CCL4L2, GPR84, HRK, MMP8, GGT5, RASGRF1.

[0043] In an embodiment, detecting the level of expression comprises detecting nucleic acids encoded by each of the plurality of genes.

[0044] In another embodiment, detecting the level of expression comprises one or more of a polymerase chain reaction (PCR) amplification method, a non-PCR based amplification method, reverse transcriptase-(RT) PCR, Q-beta replicase amplification, ligase chain reaction, signal amplification (Ampliprobe), light cycling, differential display, Northern analysis, hybridization, microarray analysis, DNA sequencing, Ref-Seq, MassArray analysis and MALDI-TOF mass spectrometry.

[0045] In a further embodiment, determining the level of expression comprises isolating mRNA from the biological sample, reverse transcribing the mRNA to generate cDNA products and contacting the cDNA products with a microarray comprising a plurality of polynucleotide probes capable of hybridizing to a plurality of cDNAs that are complementary to a plurality of mRNAs expressed from the plurality of genes.

[0046] In another embodiment, the biological sample comprises blood, plasma, serum, tissue, amniotic fluid, saliva, urine, stool, bronchoalveolar lavage fluid, cerebrospinal fluid or skin cells.

[0047] In another embodiment is provided a method for treating sepsis in a subject, the method comprising: a) detecting a specific endotype gene signature for the subject according to a method as described herein, wherein a difference between the sample gene signature and the reference gene signature indicates that the subject has sepsis or is at risk of developing sepsis, and b) if the subject has sepsis or, is at risk of developing sepsis, administering to the subject an effective amount of one or more medicines that act specifically against the mechanisms associated with the endotype.

[0048] In another embodiment is provided a method for identifying a candidate agent for the treatment of sepsis, the method comprising: a) contacting a sepsis endotype cell with a test agent, b) detecting the level of expression for each of a plurality of signature genes from a specific endotype in the endotoxin tolerant cell to provide an expression signature, wherein the plurality of genes is selected from **NPS signature:** AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3,

ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, XCR1; **INF signature:** BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, YPEL4; **IHD signature:** ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, TRIM2; **IFN signature:** ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, LAMP3; **ADA signature:** CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, TTC21A, and c) selecting the test agent as a candidate agent for treatment of sepsis when the expression signature substantially corresponds with the reference signature.

[0049] Other features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating embodiments of the disclosure, are given by way of illustration only and the scope of the claims should not be limited by these embodiments, but should rather be given the broadest interpretation consistent with the description as a whole.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] The embodiments of the disclosure will now be described in greater detail with reference to the attached drawings, in which:

[0051] FIG. 1 shows a general scheme for collection of samples according to an example of the present disclosure. One hundred and fifteen (115) suspected sepsis patients were recruited within the first two hours of admission from two ERs. Similarly, 82 patients were recruited within the first day of ICU admission, with patients suspected of Covid-19 infection.

[0052] FIG. 2 shows the biological characterization of the Neutrophilic-Suppressive (NPS), Inflammatory (INF), Innate Host Defence (IHD), Interferon (IFN), and Adaptive (ADA) endotypes. After separation of patients by their blood transcriptome into 5 endotypes, functional enrichment was performed by identifying pathways overrepresented within the genes for each endotype for both up- and down- regulated differently expressed (DE) genes, comparing each endotype to healthy controls (Fold change ≥ 2 ; Benjamini-Hochberg adjusted P value ≤ 0.01). The ratio of each dysregulated pathway was the total number of DE genes divided by the pathway size (total number of proteins in each pathway). We focused here on pathways annotated to adaptive immune, innate immune, and cytokine signaling processes.

[0053] FIG. 3 shows cell composition analysis of, from left to right in each chart: NPS, INF, IHD, IFN, and ADA endotypes for neutrophils (top left chart); monocytes (top right chart); CD4+ T cells (middle left chart); CD8+ T cells (middle right chart); and plasma B cells (lower left chart). Cell proportions were estimated by the cell composition deconvoluting program CIBERSORT for each endotype.

[0054] FIG. 4 shows clinical characterization of the NPS, INF, IHD, IFN, and ADA endotypes: selected clinical symptomology and outcomes and their distributions (top); and organ failure probability within 28 days of ER admission (bottom). Clinical measures were compared between clusters using non-parametric comparison of rank statistics (Kruskal-Wallis test) and Chi-square tests depending on variable type. Dunn's Posthoc tests for Kruskal-Wallis tests: #

$p < 0.05$ vs. IHD. * $p < 0.05$ vs. IFN. + $p < 0.05$ vs. ADA. ^ $p < 0.05$ vs. INF. The Kaplan Meier graph for 28-day organ failure free probability (lower probability means more organ failure) as a function of time was compared statistically using the log rank test.

[0055] FIGs. 5-9 show minimally connected first order protein:protein interaction networks (drawn using the program NetworkAnalyst) of the unique endotype gene expression signatures (DE in the given endotype but not in any other endotype) for the NPS (FIG. 5), INF (FIG. 6), IHD (FIG. 7), IFN (FIG. 8) and ADA (FIG. 9) endotypes.

[0056] FIG. 10 shows a heatmap depicting the expression of genes with respect to, from left to right: NPS, INF, IHD, IFN and ADA endotypes. Each of the darker blocks running up the diagonal represents the DE genes defining that particular endotype. These genes were identified by a multinomial regression model that relied on just 88 genes to predict endotype status. These are listed in Table 3.

[0057] FIG. 11 shows endotype classification of severe non-Covid and severe Covid-19 ICU sepsis patients. Shown is a heatmap depicting gene set variation analysis (GSVA) enrichment statistics in ICU patients for each endotype signature based on a subset of 40 genes from the list in Table 3.

[0058] FIG. 12 shows pathway enrichment of up- and down- regulated genes comparing ICU endotypes to healthy controls.

[0059] FIG. 13 shows the clinical characteristics (from left to right: ICU stay days, SOFA at 24 hours and SOFA at 72 hours) for severe non-Covid and severe Covid-19 ICU sepsis patients according to endotype, from left to right in each chart: NPS, INF, IHD and IFT (top row); Covid-19 positivity and mortality in the ICU validation cohort for predicted endotypes, from left to right in each chart: NPS, INF, IHD and IFN (middle row); and survival probability within 28 days of admission depicted using a Kaplan Meier analysis (bottom). The P value is based on a log rank test.

[0060] FIG. 14 shows the pathway enrichment in severe non-Covid and severe Covid-19 ICU sepsis patients: Pathway enrichment of up- and down- regulated genes directly comparing Covid-19 positive to negative patients (top); and a heatmap depicting GSVA enrichment statistics in Covid-19 PCR positive and negative patients for two of the endotype signatures (bottom, partial rearrangement of FIG. 11).

[0061] FIG. 15 shows pathway enrichment for DE genes defining each severity group when compared to healthy controls (n = 9). Functional enrichment was performed on up- and down- regulated DE genes separately.

DETAILED DESCRIPTION

I. Definitions

[0062] Unless otherwise indicated, the definitions and embodiments described in this and other sections are intended to be applicable to all embodiments and aspects of the disclosure herein described for which they would be understood to be suitable by a person skilled in the art.

[0063] As used herein, the terms “comprising” (and any form thereof, such as “comprise” and “comprises”), “having” (and any form thereof, such as “have” and “has”), “including” (and any form thereof, such as “include” and “includes”) and “containing” (and any form thereof, such as “contain” and “contains”) and grammatical variations thereof, are inclusive or open-ended and do not exclude additional, unrecited features, elements, components, groups, integers and/or steps. The term “consisting essentially of” as used herein, is intended to specify the presence of the stated features, elements, components, groups, integers and/or steps as well as those that do not materially affect the basic and novel characteristic(s) of these features, elements, components, groups, integers and/or steps. The term “consisting of” and its derivatives are intended to be close-ended terms that specify the presence of the stated features, elements, components, groups, integers and/or steps, and also exclude the presence of other unstated features, elements, components, groups, integers and/or steps.

[0064] As used herein, terms of degree such as “substantially”, “about” and “approximately” mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of at least $\pm 5\%$ or $\pm 10\%$ of the modified term if this deviation would not negate the meaning of the term it modifies.

[0065] As used in this disclosure, the singular forms “a”, “an” and “the” include plural references unless the content clearly dictates otherwise.

[0066] The term “plurality” as used herein means more than one, for example, two or more, three or more, four or more, and the like.

[0067] The term “and/or” as used herein means that the listed items are present, or used, individually or in combination. In effect, this term means that “at least one of” or “one or more” of the listed items is present or used.

[0068] The term “sepsis” as used herein refers to a clinical response to a suspected or proven infection. Sepsis may be defined, for example, as including two or more of the following symptoms: tachypnea or tachycardia; leukocytosis or leukopenia; and hyperthermia or hypothermia, and may manifest as a complex infectious and immunological disorder. Sepsis may be complicated by organ failure leading to severe sepsis and may require admission to an intensive care unit (ICU) and carries a higher risk of severity and death.

[0069] The term “gene” as used herein refers to a nucleic acid sequence that comprises coding sequences necessary for producing a polypeptide or precursor. Control sequences that direct and/or control expression of the coding sequences may also be encompassed by the term “gene” in some instances. The polypeptide or precursor may be encoded by a full length coding sequence or by a portion of the coding sequence. A gene may contain one or more modifications in either the coding or the untranslated regions that could affect the biological activity or the chemical structure of the polypeptide or precursor, the rate of expression, or the manner of expression control. Such modifications include, but are not limited to, mutations, insertions, deletions, and substitutions of one or more nucleotides, including single nucleotide polymorphisms that occur naturally in the population. The gene may constitute an uninterrupted coding sequence or it may include one or more subsequences. The term “gene” as used herein includes variants of the genes identified in Tables 3-6 and 8.

[0070] The sequences of the genes listed herein can readily be obtained by one of skill in the art from publicly available databases, such as but not limited to the GenBank database maintained by the National Center for Biotechnology (NCBI), for example, by searching using the provided gene symbols. These gene symbols are recognized by databases including but not limited to HGNC, Entrez Gene, UniProtKB/Swiss-Prot, OMIM, GeneLoc, and/or Ensembl; all aliases listed herein are defined by the GeneCards database.

[0071] The terms “gene expression profile” or “gene signature” and the like as used herein, refer to a group of genes expressed by a particular cell or tissue type wherein expression of the genes taken together, or the differential expression of such genes, is indicative and/or predictive of a certain condition, such as sepsis.

[0072] The term “differential expression” as used herein refers to quantitative and/or qualitative differences in the expression of a gene or a protein in diseased tissue or cells versus, e.g., normal tissue or cells. For example, a differentially expressed gene may have its expression activated or completely inactivated in normal versus disease conditions, or may be up-regulated (over-expressed) or down-regulated (under-expressed) in a disease condition versus a normal condition. Stated another way, a gene or protein is differentially expressed when expression of the gene or protein occurs at a higher or lower level in the diseased tissues or cells of a subject (e.g., a human patient) relative to the level of its expression in the normal (disease-free) tissues or cells of the subject (e.g., the human patient) and/or control tissues or cells.

[0073] The term “nucleic acid” as used herein, refers to a molecule comprised of one or more nucleotides, for example, ribonucleotides, deoxyribonucleotides, or both. The term includes monomers and polymers of nucleotides, with the nucleotides being bound together, in the case of the polymers, in sequence, typically via 5' to 3' linkages, although alternative linkages are also contemplated in some embodiments. The nucleotide polymers may be single or double-stranded. The nucleotides may be naturally occurring or may be synthetically produced analogs that are capable of forming base-pair relationships with naturally occurring base pairs. Examples of non-naturally occurring bases that are capable of forming base-pairing relationships include, but are not limited to, aza and deaza pyrimidine analogs, aza and deaza purine analogs, and other heterocyclic base analogs, wherein one or more of the carbon and nitrogen atoms of the pyrimidine rings have been substituted by heteroatoms, e.g., oxygen, sulphur, selenium, phosphorus, and the like.

[0074] The term “corresponding to” and grammatical variations thereof as used herein with respect to a nucleic acid sequence indicates that the nucleic acid sequence is identical to all or a portion of a reference nucleic acid sequence. In contradistinction, the term “complementary to” is used herein to indicate that the nucleic acid sequence is identical to all or a portion of the complementary strand of the reference nucleic acid sequence. For illustration, the nucleic acid sequence “TATAC” corresponds to a reference sequence “TATAC” and is complementary to a reference sequence “GTATA.”

[0075] The term “subject” as used herein includes all members of the animal kingdom including mammals, and optionally refers to humans. In an embodiment, the subject is human.

[0076] The term “biological sample” refers to a sample obtained from a subject (e.g., a human patient) or from components (e.g., cells) of a subject. The sample may be of any relevant

biological tissue or fluid. The sample may be a “clinical sample” which is a sample derived from a patient. Such samples include, but are not limited to, sputum, blood, blood cells (e.g., white cells), nasal brushings, throat swabs, urine, amniotic fluid, plasma, semen, bone marrow, and tissue or fine needle biopsy samples, urine, peritoneal fluid, and pleural fluid, or cells therefrom. Biological samples may also include sections of tissues such as frozen sections taken for histological purposes. A biological sample may also be referred to as a “patient sample.”

[0077] As used herein, the term “effective amount” and the like means an amount effective, at dosages and for periods of time necessary to achieve a desired result. For example, in the context of treating sepsis, an effective amount e.g. of the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype is an amount that, for example, reduces the sepsis compared to the sepsis without administration of the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype. Effective amounts may vary according to factors such as the disease state, age, sex, weight and/or species of the subject. The amount of a given therapy or combination thereof that will correspond to such an amount will vary depending upon various factors, such as the given therapy or combination thereof, the pharmaceutical formulation, the route of administration or use, the identity of the subject being treated, and the like, but can nevertheless be routinely determined by one skilled in the art.

[0078] The terms “to treat”, “treating” and “treatment” and the like as used herein and as is well understood in the art, means an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to alleviation or amelioration of one or more symptoms of sepsis, diminishment of the extent of the sepsis, stabilized (i.e., not worsening) of the sepsis, delay or slowing of the progression of the sepsis, and/or amelioration or palliation of the disease state of the sepsis.

[0079] It is contemplated that any embodiment discussed herein can be implemented with respect to any of the disclosed methods, uses or compositions of the invention, and *vice versa*.

II. Methods and Uses

[0080] An object of the present disclosure was to identify endotypes at first clinical presentation, where patients show broad clinical traits and final sepsis diagnoses are not established. To achieve this, next generation RNA-Seq was used to perform accurate whole blood transcriptomics and clinical metadata was collected in a cohort consisting of ER

patients. Unsupervised consensus clustering was used to identify five endotypes with robust mechanistic and clinical characteristics. Also recruited, on the first day of ICU admission, was a second cohort of severely ill patients some of whom had SARS-CoV-2 infection. Candidate gene-expression signatures identifying endotype status, and a gene expression signature predicting the onset of sepsis were validated for future clinical use.

[0081] Whole blood and clinical data profiles were collected from 115 patients in emergency rooms (ERs) from two different countries/continents (Netherlands and Canada) and 82 patients in one intensive care unit (ICU; Canada) and compared to 9 healthy controls from the same sources. ER patients were recruited into the study within two hours of admission if the attending clinician suspected possible sepsis and observed two or more systemic inflammatory response syndrome (SIRS) symptoms. Blood RNA-Seq transcriptomic profiles were analyzed to identify early mechanistic gene expression signatures useful for triage. Machine learning was used to uncover endotypes (subdivisions of the disease with distinct pathophysiological mechanisms and clinical responses) and to validate corresponding gene signatures with prognostic value. Patients with early sepsis exhibited evidence of five mechanistically distinct endotypes, namely Neutrophilic-Suppressive (NPS), Inflammatory (INF), Innate Host Defense (IHD), Interferon (IFN), and Adaptive (ADA) endotypes each of which was defined by a set of approximately 200 genes that were uniquely differentially expressed in patients with the given endotype but not in any of the other endotypes. Subsequently, a classification tool employing 88 genes was used to accurately predict endotype status in a validation cohort, while another 247 showed suitable differential expression in the given endotypes to be useful in differentiation between endotypes. This included 82 ICU patients from Toronto, Canada, of which 27 patients had Covid-19-mediated sepsis. Subsets of these 88 genes can be used, for example, to accurately identify specific endotypes (including those causing higher severity), through gene expression analysis of patient blood. Across all patients, the NPS and INF endotypes showed the worse prognosis, with higher organ dysfunction scores and severity. Furthermore, a predictive severity signature was demonstrated. This provides a method to triage a diverse spectrum of prospective pre-diagnosis sepsis patients in the emergency room (ER) into 5 mechanism-based endotypes based on the underlying molecular responses, and shows that endotypes are associated with specific clinical characteristics and outcomes. These endotypes remain detectable in the intensive care unit (ICU), indicating they are stable.

[0082] The separation of patients into endotypes has prognostic value and can inform a physician regarding future severity, enabling only the worst afflicted patients to receive the most intensive treatments and driving the potential for personalized medicines directed at treating the underlying mechanisms for the specific endotype that a patient fits into. Furthermore, signatures predicting enhanced severity independent of endotype status are described. Accordingly, the present disclosure includes methods comprising a unique set of DNA sequences that, for example, may enable the separation of sepsis patients into distinct mechanistic and/or clinically meaningful clusters and/or the prediction of mortality risk and/or sequential organ failure assessment (SOFA) score/organ failure, for example, at first clinical presentation.

[0083] Accordingly, the present disclosure includes a method for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising:

- (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and
- (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype,

wherein the sample gene signature and reference gene signature comprise an NPS endotype sub-signature, an INF endotype sub-signature, an IHD endotype sub-signature, an IFN endotype sub-signature, an ADA endotype sub-signature or combinations thereof,

wherein the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, and XCR1;

wherein the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYPA, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC4A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, and YPEL4;

wherein the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, and TRIM2;

wherein the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, and LAMP3; and

wherein the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, USP18, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, and TTC21A.

[0084] In an embodiment, the sample gene signature and the reference gene signature comprise, consist essentially of or consist of the NPS endotype sub-signature, the INF endotype

sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, and the ADA endotype sub-signature. In another embodiment, the sample gene signature and the reference gene signature comprise the NPS endotype sub-signature, the INF endotype sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, and the ADA endotype sub-signature.

[0085] In some embodiments, NPS endotype sub-signature, INF endotype sub-signature, IHD endotype sub-signature, IFN endotype sub-signature, ADA endotype sub-signature or combinations thereof may include all genes listed herein in respect to the respective NPS endotype sub-signature, INF endotype sub-signature, IHD endotype sub-signature, IFN endotype sub-signature, ADA endotype sub-signature or combinations thereof. Alternatively, in some embodiments, the NPS endotype sub-signature, INF endotype sub-signature, IHD endotype sub-signature, IFN endotype sub-signature, ADA endotype sub-signature may include a single gene, a pair, or a multiple (e.g., three genes, four genes, five genes, six genes, seven genes, eight genes, nine genes, ten genes, etc.) that is a subset of the genes listed herein in respect to the NPS endotype sub-signature, INF endotype sub-signature, IHD endotype sub-signature, IFN endotype sub-signature, ADA endotype sub-signature. In an embodiment, the NPS endotype sub-signature, INF endotype sub-signature, IHD endotype sub-signature, IFN endotype sub-signature, ADA endotype sub-signature or combinations thereof may include all genes listed for the respective sub-signature or combinations thereof in the 88 gene signature of Table 3. In another embodiment, the NPS endotype sub-signature, INF endotype sub-signature, IHD endotype sub-signature, IFN endotype sub-signature, ADA endotype sub-signature or combinations thereof may include all genes listed for the respective sub-signature or combinations thereof in the subset of 40 genes from the list in Table 3, namely NSUN7, ATP9A, PFKFB2, ARG1, ANXA3, IL1R1, GADD45A, MLLT1, MIR646HG, AGFG1, KREMEN1, RIOK3, BNIP3L, TLCD4, SPTA1, TSPAN5, GLRX5, IFIT1B, ADAM23, MAP7, CACNA2D3, GPR34, GRAMD1C, PLCB1, DYNC2H1, TPRG1, ZNF600, TPPP3, PLEKHO1, APOL1, EPSTI1, RSAD2, IFITM3, SERPING1, GTSE1, CDC45, CENPF, KIF14, PDIA4, and KIF15.

[0086] In an embodiment, the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In another embodiment, the NPS endotype sub-signature consists essentially of genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14,

KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In a further embodiment, the NPS endotype sub-signature consists of genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In another embodiment, the NPS endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In another embodiment, the NPS endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 genes selected from the group consisting of: NSUN7, ATP9A, PFKFB2, ARG1, ANXA3, IL1R1, GADD45A, MLLT1, MIR646HG, AGFG1 and KREMEN1.

[0087] In an embodiment, the NPS endotype sub-signature comprises: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In another embodiment of the present disclosure, the NPS endotype sub-signature consists essentially of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In a further embodiment, the NPS endotype sub-signature consists of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19. In another embodiment, the NPS endotype sub-signature comprises: NSUN7, ATP9A, PFKFB2, ARG1, ANXA3, IL1R1, GADD45A, MLLT1, MIR646HG, AGFG1 and KREMEN1. In another embodiment, the NPS endotype sub-signature consists essentially of: NSUN7, ATP9A, PFKFB2, ARG1, ANXA3, IL1R1, GADD45A, MLLT1, MIR646HG, AGFG1 and KREMEN1. In another embodiment, the NPS endotype sub-signature consists of: NSUN7, ATP9A, PFKFB2, ARG1, ANXA3, IL1R1, GADD45A, MLLT1, MIR646HG, AGFG1 and KREMEN1.

[0088] In an embodiment, the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In another

embodiment, the INF endotype sub-signature consists essentially of genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In a further embodiment, the INF endotype sub-signature consists of genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In another embodiment, the INF endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In another embodiment, the INF endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6 or 7 genes selected from the group consisting of: RIOK3, BNIP3L, TLCD4, SPTA1, TSPAN5, GLRX5, and IFIT1B.

[0089] In an embodiment, the INF endotype sub-signature comprises: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In another embodiment of the present disclosure, the INF endotype sub-signature consists essentially of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In a further embodiment, the INF endotype sub-signature consists of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2. In another embodiment, the INF endotype sub-signature comprises: RIOK3, BNIP3L, TLCD4, SPTA1, TSPAN5, GLRX5, and IFIT1B. In another embodiment, the INF endotype sub-signature consists essentially of: RIOK3, BNIP3L, TLCD4, SPTA1, TSPAN5, GLRX5, and IFIT1B. In another embodiment, the INF endotype sub-signature consists of: RIOK3, BNIP3L, TLCD4, SPTA1, TSPAN5, GLRX5, and IFIT1B.

[0090] In an embodiment, the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In another embodiment, the IHD endotype sub-signature consists essentially of genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In a further embodiment, the IHD endotype sub-signature consists of genes selected from the group

consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In another embodiment, the IHD endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In another embodiment, the IHD endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 genes selected from the group consisting of: ADAM23, MAP7, CACNA2D3, GPR34, GRAMD1C, PLCB1, DYNC2H1, TPRG1, ZNF600, and TPPP3.

[0091] In an embodiment, the IHD endotype sub-signature comprises: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In another embodiment, the IHD endotype sub-signature consists essentially of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In a further embodiment, the IHD endotype sub-signature consists of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600. In another embodiment, the IHD endotype sub-signature comprises: ADAM23, MAP7, CACNA2D3, GPR34, GRAMD1C, PLCB1, DYNC2H1, TPRG1, ZNF600, and TPPP3. In another embodiment, the IHD endotype sub-signature consists essentially of: ADAM23, MAP7, CACNA2D3, GPR34, GRAMD1C, PLCB1, DYNC2H1, TPRG1, ZNF600, and TPPP3. In another embodiment, the IHD endotype sub-signature consists of: ADAM23, MAP7, CACNA2D3, GPR34, GRAMD1C, PLCB1, DYNC2H1, TPRG1, ZNF600, and TPPP3.

[0092] In an embodiment, the the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In another embodiment, the IFN endotype sub-signature consists essentially of genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In a further embodiment, IFN endotype sub-signature consists of genes selected from the group consisting

of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In another embodiment, the IFN endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In another embodiment, the IFN endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5 or 6 genes selected from the group consisting of: PLEKHO1, APOL1, EPSTI1, RSAD2, IFITM3, and SERPING1.

[0093] In an embodiment, the IFN endotype sub-signature comprises: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In another embodiment, the IFN endotype sub-signature consists essentially of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In a further embodiment, the IFN endotype sub-signature consists of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC. In another embodiment, the IFN endotype sub-signature comprises: PLEKHO1, APOL1, EPSTI1, RSAD2, IFITM3, and SERPING1. In another embodiment, the IFN endotype sub-signature consists essentially of: PLEKHO1, APOL1, EPSTI1, RSAD2, IFITM3, and SERPING1. In another embodiment, the IFN endotype sub-signature consists of: PLEKHO1, APOL1, EPSTI1, RSAD2, IFITM3, and SERPING1.

[0094] In an embodiment, the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, and USP18. In another embodiment, the ADA endotype sub-signature consists essentially of genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, and USP18. In a further embodiment, the ADA endotype sub-signature consists of genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, and USP18. In another embodiment, the ADA endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B,

LGALS3BP, OTOF, PDIA4, SIGLEC1, and USP18. In another embodiment, the ADA endotype sub-signature comprises, consists essentially of or consists of 1, 2, 3, 4, 5 or 6 genes selected from the group consisting of: GTSE1, CDC45, CENPF, KIF14, PDIA4, and KIF15.

[0095] In an embodiment, the ADA endotype sub-signature comprises: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1 and USP18. In another embodiment, the ADA endotype sub-signature consists essentially of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1 and USP18. In a further embodiment, the ADA endotype sub-signature consists of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1 and USP18. In another embodiment, the ADA endotype sub-signature comprises: GTSE1, CDC45, CENPF, KIF14, PDIA4, and KIF15. In another embodiment, the ADA endotype sub-signature consists essentially of: GTSE1, CDC45, CENPF, KIF14, PDIA4, and KIF15. In another embodiment, the ADA endotype sub-signature consists of: GTSE1, CDC45, CENPF, KIF14, PDIA4, and KIF15.

[0096] In an embodiment, the reference gene signature represents a standard level of expression of the genes comprised therein and a difference between a sample endotype sub-signature and a reference endotype sub-signature indicates that the subject has the sepsis mechanistic endotype corresponding to that sub-signature.

[0097] The present disclosure also includes a method for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising:

- (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and
- (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype,

wherein the sample gene signature and reference gene signature comprise an NPS endotype signature pair, an INF endotype signature pair, an IHD endotype signature pair, an IFN endotype signature pair, an ADA endotype signature pair or combinations thereof,

wherein the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1,

MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, MLLT1/KLF14, ADAMTS3/PCOLCE2, ADAMTS3/ZDHHC19, ADAMTS3/SLC51A, ADAMTS3/HPGD, ADAMTS3/SEMA6B, ADAMTS3/EFNA1, ADAMTS3/AGFG1, ADAMTS3/NSUN7, ADAMTS3/TNFAIP8L3, ADAMTS3/KREMEN1, ADAMTS3/ORM2, ADAMTS3/MIR646HG, ADAMTS3/KLF14, AGFG1/NSUN7, AGFG1/TNFAIP8L3, AGFG1/KREMEN1, AGFG1/ORM2, AGFG1/MIR646HG, AGFG1/KLF14, ANXA3/GPR84, ANXA3/OLAH, ANXA3/ADAMTS3, ANXA3/PCOLCE2, ANXA3/ZDHHC19, ANXA3/SLC51A, ANXA3/HPGD, ANXA3/SEMA6B, ANXA3/EFNA1, ANXA3/AGFG1, ANXA3/NSUN7, ANXA3/TNFAIP8L3, ANXA3/KREMEN1, ANXA3/ORM2, ANXA3/MIR646HG, ANXA3/KLF14, ARG1/PFKFB2, ARG1/MLLT1, ARG1/ANXA3, ARG1/GPR84, ARG1/OLAH, ARG1/ADAMTS3, ARG1/PCOLCE2, ARG1/ZDHHC19, ARG1/SLC51A, ARG1/HPGD, ARG1/SEMA6B, ARG1/EFNA1, ARG1/AGFG1, ARG1/NSUN7, ARG1/TNFAIP8L3, ARG1/KREMEN1, ARG1/ORM2, ARG1/MIR646HG, ARG1/KLF14, ATP9A/EPB41L4B, ATP9A/IL1R1, ATP9A/GADD45A, ATP9A/ARG1, ATP9A/PFKFB2, ATP9A/MLLT1, ATP9A/ANXA3, ATP9A/GPR84, ATP9A/OLAH, ATP9A/ADAMTS3, ATP9A/PCOLCE2, ATP9A/ZDHHC19, ATP9A/SLC51A, ATP9A/HPGD, ATP9A/SEMA6B, ATP9A/EFNA1, ATP9A/AGFG1, ATP9A/NSUN7, ATP9A/TNFAIP8L3, ATP9A/KREMEN1, ATP9A/ORM2, ATP9A/MIR646HG, ATP9A/KLF14, EFNA1/AGFG1, EFNA1/NSUN7, EFNA1/TNFAIP8L3, EFNA1/KREMEN1, EFNA1/ORM2, EFNA1/MIR646HG, EFNA1/KLF14, EPB41L4B/IL1R1, EPB41L4B/GADD45A, EPB41L4B/ARG1, EPB41L4B/PFKFB2, EPB41L4B/MLLT1, EPB41L4B/ANXA3, EPB41L4B/GPR84, EPB41L4B/OLAH, EPB41L4B/ADAMTS3, EPB41L4B/PCOLCE2, EPB41L4B/ZDHHC19, EPB41L4B/SLC51A, EPB41L4B/HPGD, EPB41L4B/SEMA6B, EPB41L4B/EFNA1, EPB41L4B/AGFG1, EPB41L4B/NSUN7, EPB41L4B/TNFAIP8L3, EPB41L4B/KREMEN1, EPB41L4B/MIR646HG, EPB41L4B/KLF14, GADD45A/ARG1, GADD45A/PFKFB2, GADD45A/MLLT1, GADD45A/ANXA3, GADD45A/GPR84, GADD45A/OLAH, GADD45A/ADAMTS3, GADD45A/PCOLCE2, GADD45A/ZDHHC19, GADD45A/SLC51A, GADD45A/HPGD, GADD45A/SEMA6B, GADD45A/EFNA1, GADD45A/AGFG1, GADD45A/NSUN7, GADD45A/TNFAIP8L3, GADD45A/KREMEN1, GADD45A/ORM2, GADD45A/MIR646HG, GADD45A/KLF14, GPR84/OLAH, GPR84/ADAMTS3, GPR84/PCOLCE2, GPR84/ZDHHC19, GPR84/SLC51A,

GPR84/HPGD, GPR84/SEMA6B, GPR84/EFNA1, GPR84/AGFG1, GPR84/NSUN7, GPR84/TNFAIP8L3, GPR84/KREMEN1, GPR84/ORM2, GPR84/MIR646HG, GPR84/KLF14, HPGD/SEMA6B, HPGD/EFNA1, HPGD/AGFG1, HPGD/NSUN7, HPGD/TNFAIP8L3, HPGD/KREMEN1, HPGD/ORM2, HPGD/MIR646HG, HPGD/KLF14, IL1R1/GADD45A, IL1R1/ARG1, IL1R1/PFKFB2, IL1R1/MLLT1, IL1R1/ANXA3, IL1R1/GPR84, IL1R1/OLAH, IL1R1/ADAMTS3, IL1R1/PCOLCE2, IL1R1/ZDHHC19, IL1R1/SLC51A, IL1R1/HPGD, IL1R1/SEMA6B, IL1R1/EFNA1, IL1R1/AGFG1, IL1R1/NSUN7, IL1R1/TNFAIP8L3, IL1R1/KREMEN1, IL1R1/ORM2, IL1R1/MIR646HG, IL1R1/KLF14, KREMEN1/ORM2, KREMEN1/MIR646HG, KREMEN1/KLF14, MIR646HG/KLF14, MLLT1/ANXA3, MLLT1/GPR84, MLLT1/OLAH, MLLT1/ADAMTS3, MLLT1/PCOLCE2, MLLT1/ZDHHC19, MLLT1/SLC51A, MLLT1/HPGD, MLLT1/SEMA6B, MLLT1/EFNA1, MLLT1/AGFG1, MLLT1/NSUN7, MLLT1/TNFAIP8L3, MLLT1/KREMEN1, MLLT1/ORM2, MLLT1/MIR646HG, MLLT1/KLF14, NSUN7/TNFAIP8L3, NSUN7/KREMEN1, NSUN7/ORM2, NSUN7/MIR646HG, NSUN7/KLF14, OLAH/ADAMTS3, OLAH/PCOLCE2, OLAH/ZDHHC19, OLAH/SLC51A, OLAH/HPGD, OLAH/SEMA6B, OLAH/EFNA1, OLAH/AGFG1, OLAH/NSUN7, OLAH/TNFAIP8L3, OLAH/KREMEN1, OLAH/ORM2, OLAH/MIR646HG, OLAH/KLF14, ORM2/MIR646HG, ORM2/KLF14, PCOLCE2/ZDHHC19, PCOLCE2/SLC51A, PCOLCE2/HPGD, PCOLCE2/SEMA6B, PCOLCE2/EFNA1, PCOLCE2/AGFG1, PCOLCE2/NSUN7, PCOLCE2/TNFAIP8L3, PCOLCE2/KREMEN1, PCOLCE2/ORM2, PCOLCE2/MIR646HG, PCOLCE2/KLF14, PFKFB2/MLLT1, PFKFB2/ANXA3, PFKFB2/GPR84, PFKFB2/OLAH, PFKFB2/ADAMTS3, PFKFB2/PCOLCE2, PFKFB2/ZDHHC19, PFKFB2/SLC51A, PFKFB2/HPGD, PFKFB2/SEMA6B, PFKFB2/EFNA1, PFKFB2/AGFG1, PFKFB2/NSUN7, PFKFB2/TNFAIP8L3, PFKFB2/KREMEN1, PFKFB2/ORM2, PFKFB2/MIR646HG, PFKFB2/KLF14, SEMA6B/EFNA1, SEMA6B/AGFG1, SEMA6B/NSUN7, SEMA6B/TNFAIP8L3, SEMA6B/KREMEN1, SEMA6B/ORM2, SEMA6B/MIR646HG, SEMA6B/KLF14, SLC51A/HPGD, SLC51A/SEMA6B, SLC51A/EFNA1, SLC51A/AGFG1, SLC51A/NSUN7, SLC51A/TNFAIP8L3, SLC51A/KREMEN1, SLC51A/ORM2, SLC51A/MIR646HG, SLC51A/KLF14, TNFAIP8L3/KREMEN1, TNFAIP8L3/ORM2, TNFAIP8L3/MIR646HG, TNFAIP8L3/KLF14, ZDHHC19/SLC51A, ZDHHC19/HPGD, ZDHHC19/SEMA6B, ZDHHC19/EFNA1, ZDHHC19/AGFG1, ZDHHC19/NSUN7,

ZDHHC19/TNFAIP8L3, ZDHHC19/KREMEN1, ZDHHC19/ORM2,
ZDHHC19/MIR646HG, and ZDHHC19/KLF14;

wherein the INF endotype signature pair is selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, SPTA1/FECH, ANKRD22/GLRX5, ANKRD22/GYP A, ANKRD22/IFIT1B, ANKRD22/ITLN1, ANKRD22/KLHDC8A, ANKRD22/RHCE, ANKRD22/RNF182, ANKRD22/SPTA1, ANKRD22/THEM5, ANKRD22/TSPAN5, APOL4/BNIP3L, APOL4/CA1, APOL4/DYRK3, APOL4/FAM83A, APOL4/GLRX5, APOL4/GYP A, APOL4/IFIT1B, APOL4/ITLN1, APOL4/KLHDC8A, APOL4/RHAG, APOL4/RHCE, APOL4/RIOK3, APOL4/RNF182, APOL4/SPTA1, APOL4/THEM5, APOL4/TLCD4, APOL4/TMCC2, APOL4/TSPAN5, APOL4/TSPO2, BNIP3L/ANKRD22, BNIP3L/CA1, BNIP3L/CARD17, BNIP3L/CD274, BNIP3L/DYRK3, BNIP3L/FAM83A, BNIP3L/GBP5, BNIP3L/GLRX5, BNIP3L/GYP A, BNIP3L/IFIT1B, BNIP3L/ITLN1, BNIP3L/KLHDC8A, BNIP3L/P2RY14, BNIP3L/RHAG, BNIP3L/RHCE, BNIP3L/RNF182, BNIP3L/SPTA1, BNIP3L/TFEC, BNIP3L/THEM5, BNIP3L/TLCD4, BNIP3L/TMCC2, BNIP3L/TSPAN5, BNIP3L/TSPO2, CA1/ANKRD22, CA1/CARD17, CA1/DYRK3, CA1/FAM83A, CA1/GBP5, CA1/GLRX5, CA1/GYP A, CA1/IFIT1B, CA1/ITLN1, CA1/KLHDC8A, CA1/P2RY14, CA1/RHCE, CA1/RNF182, CA1/SPTA1, CA1/THEM5, CA1/TLCD4, CA1/TSPAN5, CD274/CA1, CD274/DYRK3, CD274/FAM83A, CD274/GLRX5, CD274/GYP A, CD274/IFIT1B, CD274/ITLN1, CD274/KLHDC8A, CD274/RHCE, CD274/RNF182, CD274/SPTA1, CD274/THEM5, CD274/TLCD4, CD274/TMCC2, CD274/TSPAN5, DYRK3/ANKRD22, DYRK3/CARD17, DYRK3/FAM83A, DYRK3/GBP5, DYRK3/GLRX5, DYRK3/GYP A, DYRK3/IFIT1B, DYRK3/ITLN1, DYRK3/KLHDC8A, DYRK3/P2RY14, DYRK3/RHCE, DYRK3/RNF182, DYRK3/SPTA1, DYRK3/THEM5, DYRK3/TLCD4, DYRK3/TSPAN5, FAM83A/ANKRD22, FAM83A/CARD17, FAM83A/GBP5, FAM83A/GLRX5, FAM83A/GYP A, FAM83A/IFIT1B, FAM83A/ITLN1, FAM83A/KLHDC8A, FAM83A/P2RY14, FAM83A/RHCE, FAM83A/RNF182, FAM83A/SPTA1, FAM83A/THEM5, FAM83A/TLCD4, FAM83A/TSPAN5, FECH/ANKRD22, FECH/APOL4, FECH/BNIP3L, FECH/CA1, FECH/CARD17, FECH/CD274, FECH/DYRK3, FECH/FAM83A, FECH/GBP5, FECH/GLRX5, FECH/GYP A, FECH/IFIT1B, FECH/ITLN1, FECH/KLHDC8A, FECH/P2RY14, FECH/RHAG, FECH/RHCE, FECH/RIOK3, FECH/RNF182, FECH/SPTA1, FECH/TFEC, FECH/THEM5, FECH/TLCD4, FECH/TMCC2,

FECH/TSPAN5, FECH/TSPO2, GBP5/GLRX5, GBP5/GYP A, GBP5/IFIT1B, GBP5/ITLN1, GBP5/KLHDC8A, GBP5/RHCE, GBP5/RNF182, GBP5/SPTA1, GBP5/THEM5, GBP5/TSPAN5, GLRX5/CARD17, GLRX5/IFIT1B, GLRX5/RHCE, GLRX5/THEM5, GYP A/CARD17, GYP A/GLRX5, GYP A/IFIT1B, GYP A/ITLN1, GYP A/P2RY14, GYP A/RHCE, GYP A/RNF182, GYP A/THEM5, IFIT1B/CARD17, ITLN1/CARD17, ITLN1/GLRX5, ITLN1/IFIT1B, ITLN1/RHCE, ITLN1/RNF182, ITLN1/THEM5, KLHDC8A/CARD17, KLHDC8A/GLRX5, KLHDC8A/GYP A, KLHDC8A/IFIT1B, KLHDC8A/ITLN1, KLHDC8A/P2RY14, KLHDC8A/RHCE, KLHDC8A/RNF182, KLHDC8A/SPTA1, KLHDC8A/THEM5, KLHDC8A/TSPAN5, P2RY14/GLRX5, P2RY14/IFIT1B, P2RY14/ITLN1, P2RY14/RHCE, P2RY14/RNF182, P2RY14/THEM5, RHAG/ANKRD22, RHAG/CA1, RHAG/CARD17, RHAG/CD274, RHAG/DYRK3, RHAG/FAM83A, RHAG/GBP5, RHAG/GLRX5, RHAG/GYP A, RHAG/IFIT1B, RHAG/ITLN1, RHAG/KLHDC8A, RHAG/P2RY14, RHAG/RHCE, RHAG/RNF182, RHAG/SPTA1, RHAG/THEM5, RHAG/TLCD4, RHAG/TMCC2, RHAG/TSPAN5, RHAG/TSPO2, RHCE/CARD17, RHCE/IFIT1B, RHCE/THEM5, RIOK3/ANKRD22, RIOK3/BNIP3L, RIOK3/CA1, RIOK3/CARD17, RIOK3/CD274, RIOK3/DYRK3, RIOK3/FAM83A, RIOK3/GBP5, RIOK3/GLRX5, RIOK3/GYP A, RIOK3/IFIT1B, RIOK3/ITLN1, RIOK3/KLHDC8A, RIOK3/P2RY14, RIOK3/RHAG, RIOK3/RHCE, RIOK3/RNF182, RIOK3/SPTA1, RIOK3/TFEC, RIOK3/THEM5, RIOK3/TLCD4, RIOK3/TMCC2, RIOK3/TSPAN5, RIOK3/TSPO2, RNF182/CARD17, RNF182/GLRX5, RNF182/IFIT1B, RNF182/RHCE, RNF182/THEM5, SPTA1/CARD17, SPTA1/GLRX5, SPTA1/GYP A, SPTA1/IFIT1B, SPTA1/ITLN1, SPTA1/P2RY14, SPTA1/RHCE, SPTA1/RNF182, SPTA1/THEM5, SPTA1/TSPAN5, TFEC/CA1, TFEC/DYRK3, TFEC/FAM83A, TFEC/GLRX5, TFEC/GYP A, TFEC/IFIT1B, TFEC/ITLN1, TFEC/KLHDC8A, TFEC/RHAG, TFEC/RHCE, TFEC/RNF182, TFEC/SPTA1, TFEC/THEM5, TFEC/TLCD4, TFEC/TMCC2, TFEC/TSPAN5, TFEC/TSPO2, THEM5/CARD17, THEM5/IFIT1B, TLCD4/ANKRD22, TLCD4/CARD17, TLCD4/GBP5, TLCD4/GLRX5, TLCD4/GYP A, TLCD4/IFIT1B, TLCD4/ITLN1, TLCD4/KLHDC8A, TLCD4/P2RY14, TLCD4/RHCE, TLCD4/RNF182, TLCD4/SPTA1, TLCD4/THEM5, TLCD4/TSPAN5, TMCC2/ANKRD22, TMCC2/CA1, TMCC2/CARD17, TMCC2/DYRK3, TMCC2/FAM83A, TMCC2/GBP5, TMCC2/GLRX5, TMCC2/GYP A, TMCC2/IFIT1B, TMCC2/ITLN1, TMCC2/KLHDC8A, TMCC2/P2RY14, TMCC2/RHCE, TMCC2/RNF182, TMCC2/SPTA1, TMCC2/THEM5, TMCC2/TLCD4, TMCC2/TSPAN5, TSPAN5/CARD17,

TSPAN5/GLRX5, TSPAN5/GYP A, TSPAN5/IFIT1B, TSPAN5/ITLN1, TSPAN5/P2RY14, TSPAN5/RHCE, TSPAN5/RNF182, TSPAN5/THEM5, TSPO2/ANKRD22, TSPO2/CA1, TSPO2/CARD17, TSPO2/CD274, TSPO2/DYRK3, TSPO2/FAM83A, TSPO2/GBP5, TSPO2/GLRX5, TSPO2/GYP A, TSPO2/IFIT1B, TSPO2/ITLN1, TSPO2/KLHDC8A, TSPO2/P2RY14, TSPO2/RHCE, TSPO2/RNF182, TSPO2/SPTA1, TSPO2/THEM5, TSPO2/TLCD4, TSPO2/TMCC2, and TSPO2/TSPAN5;

wherein the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1, ADAM23/GPR34, ADAM23/MAP7, ADAM23/PLCB1, ADAM23/SPRED1, ALOX15/GPR34, ALOX15/PLCB1, ALOX15/SPRED1, BAALC/GPR34, BAALC/PLCB1, BAALC/SPRED1, CACNA2D3/DYNC2H1, CACNA2D3/GPR34, CACNA2D3/PLCB1, CACNA2D3/SPRED1, CACNA2D3/ZNF600, GPR34/DYNC2H1, GPR34/GRAMD1C, GPR34/PLCB1, GPR34/TPRG1, GPR34/ZNF600, GPR82/DYNC2H1, GPR82/GPR34, GPR82/GRAMD1C, GPR82/PLCB1, GPR82/TPRG1, GPR82/ZNF600, GRAMD1C/DYNC2H1, GRAMD1C/PLCB1, GRAMD1C/ZNF600, HRK/DYNC2H1, HRK/GPR34, HRK/MAP7, HRK/PLCB1, HRK/SPRED1, HRK/ZNF600, IL5RA/DYNC2H1, IL5RA/GPR34, IL5RA/PLCB1, IL5RA/SPRED1, IL5RA/TRIM2, MAP7/BAALC, MAP7/CACNA2D3, MAP7/DYNC2H1, MAP7/GPR34, MAP7/GPR82, MAP7/GRAMD1C, MAP7/PLCB1, MAP7/SPRED1, MAP7/TPRG1, MAP7/ZNF600, PLCB1/DYNC2H1, PLCB1/TPRG1, PLCB1/ZNF600, PRSS33/GPR34, PRSS33/PLCB1, PRSS33/SPRED1, SDC2/DYNC2H1, SDC2/GPR34, SDC2/PLCB1, SDC2/ZNF600, SIGLEC8/DYNC2H1, SIGLEC8/GPR34, SIGLEC8/MAP7, SIGLEC8/PLCB1, SIGLEC8/SPRED1, SIGLEC8/TRIM2, SMPD3/DYNC2H1, SMPD3/GPR34, SMPD3/MAP7, SMPD3/PLCB1, SMPD3/SPRED1, SMPD3/TRIM2, SPRED1/DYNC2H1, SPRED1/GPR34, SPRED1/GPR82, SPRED1/GRAMD1C, SPRED1/PLCB1, SPRED1/SDC2, SPRED1/TPRG1, SPRED1/ZNF600, TRIM2/CACNA2D3, TRIM2/DYNC2H1, TRIM2/GPR34, TRIM2/GPR82, TRIM2/GRAMD1C, TRIM2/HRK, TRIM2/MAP7, TRIM2/PLCB1, TRIM2/SDC2, TRIM2/SPRED1, TRIM2/TPRG1, and TRIM2/ZNF600;

wherein the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1,

EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1, APOL1/BATF2, APOL1/CLEC4F, APOL1/EPSTI1, APOL1/EXOC3L1, APOL1/HES4, APOL1/IFITM3, APOL1/LY6E, APOL1/RSAD2, APOL1/SEPTIN4, APOL1/SERPING1, APOL1/TPPP3, BATF2/EXOC3L1, BATF2/HES4, CLEC4F/BATF2, CLEC4F/EXOC3L1, EPSTI1/BATF2, EPSTI1/CLEC4F, EPSTI1/EXOC3L1, EPSTI1/HES4, EPSTI1/IFITM3, EPSTI1/LY6E, EPSTI1/RSAD2, EPSTI1/SERPING1, EPSTI1/TPPP3, ETV7/APOL1, ETV7/BATF2, ETV7/CLEC4F, ETV7/EPSTI1, ETV7/EXOC3L1, ETV7/HES4, ETV7/IFITM3, ETV7/LAMP3, ETV7/LY6E, ETV7/PLEKHO1, ETV7/RSAD2, ETV7/SEPTIN4, ETV7/SERPING1, ETV7/TPPP3, EXOC3L1/HES4, IFITM3/SERPING1, IFITM3/CLEC4F, IFITM3/TPPP3, IFITM3/LY6E, IFITM3/EXOC3L1, IFITM3/HES4, LAMP3/APOL1, LAMP3/BATF2, LAMP3/CLEC4F, LAMP3/EPSTI1, LAMP3/EXOC3L1, LAMP3/HES4, LAMP3/IFITM3, LAMP3/LY6E, LAMP3/RSAD2, LAMP3/SEPTIN4, LAMP3/SERPING1, LAMP3/TPPP3, LY6E/BATF2, LY6E/EXOC3L1, PLEKHO1/APOL1, PLEKHO1/BATF2, PLEKHO1/EPSTI1, PLEKHO1/EXOC3L1, PLEKHO1/IFITM3, PLEKHO1/LAMP3, PLEKHO1/RSAD2, PLEKHO1/SEPTIN4, PLEKHO1/SERPING1, RSAD2/BATF2, RSAD2/CLEC4F, RSAD2/EXOC3L1, RSAD2/HES4, RSAD2/IFITM3, RSAD2/LY6E, RSAD2/SERPING1, RSAD2/TPPP3, SEPTIN4/BATF2, SEPTIN4/CLEC4F, SEPTIN4/EPSTI1, SEPTIN4/EXOC3L1, SEPTIN4/HES4, SEPTIN4/IFITM3, SEPTIN4/LY6E, SEPTIN4/RSAD2, SEPTIN4/SERPING1, SEPTIN4/TPPP3, SERPING1/BATF2, SERPING1/CLEC4F, SERPING1/EXOC3L1, SERPING1/HES4, SERPING1/LY6E, SERPING1/TPPP3, TPPP3/BATF2, and TPPP3/EXOC3L1; and

wherein the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL, CAV1/LGALS3BP, CAV1/OTOF, CDC45/LGALS3BP, CDC45/OTOF, CENPF/KCTD14, GPRC5D/OTOF, GTSE1/LGALS3BP, GTSE1/OTOF, IGF1/LGALS3BP, IGF1/OTOF, KCTD14/KLHL14, KCTD14/PDIA4, KCTD14/TSHR, KIF14/KCTD14, LGALS3BP/CENPF, LGALS3BP/GPRC5D, LGALS3BP/IFI27, LGALS3BP/IGLL5, LGALS3BP/KCTD14, LGALS3BP/KIF14, LGALS3BP/KIF15, LGALS3BP/KLHL14, LGALS3BP/MIR155HG,

LGALS3BP/MIXL1, LGALS3BP/OTOF, LGALS3BP/PDIA4, LGALS3BP/PLAAT2, LGALS3BP/SDC1, LGALS3BP/SLC16A14, LGALS3BP/TSHR, OTOF/CENPF, OTOF/IFI27, OTOF/IGLL5, OTOF/KCTD14, OTOF/KIF14, OTOF/KIF15, OTOF/KLHL14, OTOF/MIR155HG, OTOF/MIXL1, OTOF/PDIA4, OTOF/PLAAT2, OTOF/SDC1, OTOF/SLC16A14, OTOF/TSHR, PLAAT2/KCTD14, TNFRSF17/LGALS3BP, and TNFRSF17/OTOF.

[0098] In an embodiment, the sample gene signature and the reference gene signature comprise, consist essentially of or consist of the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, and the ADA endotype signature pair. In another embodiment, the sample gene signature and the reference gene signature comprise the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, and the ADA endotype signature pair.

[0099] In an embodiment, the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, and MLLT1/KLF14. In another embodiment, the INF endotype signature pair is selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, and SPTA1/FECH. In a further embodiment, the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, and CACNA2D3/SPRED1. In another embodiment, the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, and LAMP3/SERPING1. In a further embodiment, the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, and LGALS3BP/MIXL1.

[00100] In an embodiment, the reference gene signature represents a standard level of expression of the genes comprised therein and a difference between a sample endotype signature pair and a reference endotype signature pair indicates that the subject has the sepsis mechanistic endotype corresponding to that signature pair.

[00101] The present disclosure also includes a method for predicting severity of sepsis in a subject, wherein the severity of the sepsis is selected from high severity sepsis, intermediate severity sepsis and low severity sepsis, the method comprising:

- (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and
- (b) comparing the sample gene signature with a reference gene signature to determine the severity of the sepsis in the subject,

wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5, and low severity sepsis means a SOFA score of less than 2; and

wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19.

[00102] In an embodiment of the method for predicting severity of sepsis in a subject, the plurality of genes comprises, consists essentially of or consists of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156 or 157 genes selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RRGIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19.

[00103] In an embodiment of the method for predicting severity of sepsis in a subject, the plurality of genes comprises, consists essentially of or consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, or 73 genes selected from the group consisting of AK5, ANKRD22, ARHGEF17, ASPM, ATP1B2, AURKA, BAIAP3, C1orf226, CACNB4, CCL4L2, CCN3, CD177, CD24, CENPA, CFH, CHDH, CHIT1, CKAP2L,

CLEC4C, DENND2C, DLGAP5, DNAH10, DSP, FAM20A, FBN1, G0S2, GGT5, GLB1L2, GPR84, GRAMD1C, HBM, HMGB3, HP, HRK, IQGAP3, ITGB4, KIF15, LAMB3, LCN2, LPL, LTF, MAFG, MERTK, MMP8, MMP9, MRC1, MS4A4A, NRXN2, NUF2, PHF24, PTGES, PYCR1, RAB3IL1, RETN, RPGRIP1, RRM2, SCN8A, SERPINB10, SIL1, SLC16A1, SLC39A8, SLC4A10, SLC6A19, SLC8A3, SMIM1, SPATC1, SPOP, SSBP2, TCTEX1D1, TEAD2, TLN2, TMEM255A, and TMEM45A. In another embodiment, the plurality of genes comprises, consists essentially of or consists of CCL4L2, GPR84, HRK, MMP8, GGT5, RASGRF1. In another embodiment, the plurality of genes comprises CCL4L2, GPR84, HRK, MMP8, GGT5, and RASGRF1. In a further embodiment, the plurality of genes is CCL4L2, GPR84, HRK, MMP8, GGT5, and RASGRF1.

[00104] The biological sample can comprise any suitable biological sample, the selection of which can be readily made by a person skilled in the art. In an embodiment, the biological sample comprises sputum, blood, nasal brushings, throat swabs, urine, amniotic fluid, plasma, serum, saliva, semen, bone marrow, tissue or fine needle biopsy samples, stool, bronchoalveolar lavage fluid, cerebrospinal fluid, peritoneal fluid, pleural fluid, skin, or cells therefrom. In another embodiment, the biological sample comprises blood.

[00105] Determining the level of expression for the plurality of genes can comprise any suitable method, the selection of which can be made by a person skilled in the art. For example, the expression of the genes may be determined by detection of an expression product of each gene. The expression product may be, for example, RNA, cDNA prepared from RNA and/or protein. In an embodiment, the expression product is cDNA prepared from RNA. When the expression product is RNA or cDNA, the entire sequence of the gene may be detected, or any definitive portion of the gene, for example, a sequence of 10 nucleotides or more, may be detected. Methods of detecting and quantifying expression of genes are well-known in the art and include the use of detectably labelled polynucleotide probes, antibodies, aptamers, and the like. In an embodiment, detecting the level of expression comprises detecting nucleic acids encoded by each of the plurality of genes. In an embodiment, determining the level of expression comprises one or more of a polymerase chain reaction (PCR) amplification method, a non-PCR based amplification method, reverse transcriptase-(RT) PCR, Q-beta replicase amplification, ligase chain reaction, signal amplification (Ampliprobe), light cycling, differential display, Northern analysis, hybridization, microarray analysis, DNA sequencing, RNA-Seq, MassArray analysis and MALDI-TOF mass

spectrometry. In another embodiment, determining the level of expression comprises a polymerase chain reaction (PCR) amplification method or reverse transcriptase-(RT) PCR. In another embodiment, determining the level of expression comprises a polymerase chain reaction (PCR) amplification method. In another embodiment, determining the level of expression comprises reverse transcriptase-(RT) PCR. In another embodiment, determining the level of expression comprises RNA sequencing (RNA-Seq). In an embodiment, prior to RNA-Seq, the method comprises extracting total RNA from the biological sample by any suitable method followed by preparation of cDNA libraries via any suitable method. The selection of suitable methods and means for extracting total RNA and preparation of cDNA libraries can be readily selected by a person skilled in the art.

[00106] In certain embodiments, determining the level of expression comprises the use of detectably labelled polynucleotides. The methods may further comprise one or more of isolation of nucleic acids from the biological sample, purification of the nucleic acids, reverse transcription of RNA, and/or nucleic acid amplification. In some embodiments, the polynucleotide probes used to determine the level of expression may be immobilized on a solid support, for example, as an array or microarray allowing for more rapid processing of the sample. Methods of preparing arrays and microarrays are well known in the art. In addition, a number of standard microarrays are available commercially that include probes for detecting some of the genes identified herein and thus may be suitable for use in these methods. For example, Affymetrix U133 GeneChip™ arrays (Affymetrix, Inc., Santa Clara, CA), Agilent Technologies genomic cDNA microarrays (Santa Clara, CA), and arrays available from Illumina, Inc. (San Diego, CA). These arrays have probe sets for the whole human genome immobilized on a chip, and can be used to determine up- and down-regulation of genes in test samples. Custom-made arrays and microarrays for detecting pre-selected genes are also available commercially from a number of companies. Instruments and reagents for performing gene expression analysis are commercially available (for example, the Affymetrix GeneChip™ System). In some embodiments, the expression data obtained from the analysis may then be input into an appropriate database for further analysis if necessary or desired. In some embodiments, the determining the level of expression comprises, after conversion to cDNAs, the use of Matrix-assisted laser desorption/ionization – time of flight (MALDI-TOF) mass spectrometry using, for example the Sequenom MassARRAY® system (see, for example, Kricka LJ. Clin Chem 1999; 45:453-458).

[00107] The expression of certain genes known as “housekeeping genes”, “reference genes”, or “control genes” may also be determined in the biological sample as a means of ensuring the veracity of the expression profile. Such genes are genes that are consistently expressed in many tissue types, including cancerous and normal tissues, and thus are useful to normalize gene expression profiles. Determining the expression of housekeeping genes, reference genes, or control genes in parallel with the plurality of genes, may, for example, provide further assurance that the techniques used for determination of the gene expression profile are working properly. Appropriate housekeeping genes (also referred to herein as reference genes and control genes) can be readily selected by the skilled person.

[00108] The levels of expression determined are compared to a suitable reference gene signature, which may, for example, be corresponding levels of expression in a biological sample from a healthy individual, e.g., in embodiments wherein the reference gene signature represents a standard level of expression of the genes. The comparison may include, for example, a visual inspection and/or an arithmetic or statistical comparison of measurements and may take into account expression of any reference genes. Suitable methods of comparison to determine differences in expression levels of genes are well known in the art. In an embodiment, the comparison comprises use of a trained model/classification tool.

[00109] In an embodiment, the biological sample has been obtained from the subject prior to admission in an intensive care unit (ICU). In an embodiment, the biological sample has been obtained from the subject at first clinical presentation. In a further embodiment, the biological sample has been obtained from the subject within about 2 hours of admission into an emergency room. In another embodiment, the sample has been obtained from the subject within the first day after entry into an intensive care unit (ICU).

[00110] In the examples of the present disclosure, the clear associations between endotypes and clinical symptomology and outcomes indicated that the sepsis mechanistic endotypes represent, for example, a useful tool to prognosticate patients, while their underlying mechanistic differences indicate the potential for personalized therapy. Identification of individual mechanisms in sepsis, for example has the additional benefit that it can be used to guide physicians in treating patients based on the individual features of their type of sepsis.

[00111] Accordingly, the present disclosure also includes a method of treating sepsis, the method comprising: (a) classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon

(IFN) and adaptive (ADA) endotypes by a method for classifying a subject into a sepsis mechanistic endotype of the present disclosure; and (b) administering to the subject, an effective amount of one or more therapies that act specifically against a mechanism associated with the sepsis mechanistic endotype. The present disclosure also includes a use of one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, for treatment of sepsis in a subject classified as having the sepsis mechanistic endotype by a method for classifying a subject into a sepsis mechanistic endotype of the present disclosure. The present disclosure also includes a use of one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, for preparation of a medicament for treatment of sepsis in a subject classified as having the sepsis mechanistic endotype by a method for classifying a subject into a sepsis mechanistic endotype of the present disclosure. The present disclosure further includes one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes for use to treat sepsis in a subject classified as having the sepsis mechanistic endotype by a method for classifying a subject into a sepsis mechanistic endotype of the present disclosure. The method for classifying a subject into a sepsis mechanistic endotype of the present disclosure can comprise: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype, wherein the sample gene signature and reference gene signature comprise an NPS endotype sub-signature, an INF endotype sub-signature, an IHD endotype sub-signature, an IFN endotype sub-signature, an ADA endotype sub-signature or combinations thereof, wherein the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7,

EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, and XCR1; wherein the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC4A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, and YPEL4; wherein the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, and TRIM2; wherein the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, and LAMP3; and wherein the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, USP18, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19,

LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, and TTC21A and/or comprise: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype, wherein the sample gene signature and reference gene signature comprise an NPS endotype signature pair, an INF endotype signature pair, an IHD endotype signature pair, an IFN endotype signature pair, an ADA endotype signature pair or combinations thereof, wherein the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, MLLT1/KLF14, ADAMTS3/PCOLCE2, ADAMTS3/ZDHHC19, ADAMTS3/SLC51A, ADAMTS3/HPGD, ADAMTS3/SEMA6B, ADAMTS3/EFNA1, ADAMTS3/AGFG1, ADAMTS3/NSUN7, ADAMTS3/TNFAIP8L3, ADAMTS3/KREMEN1, ADAMTS3/ORM2, ADAMTS3/MIR646HG, ADAMTS3/KLF14, AGFG1/NSUN7, AGFG1/TNFAIP8L3, AGFG1/KREMEN1, AGFG1/ORM2, AGFG1/MIR646HG, AGFG1/KLF14, ANXA3/GPR84, ANXA3/OLAH, ANXA3/ADAMTS3, ANXA3/PCOLCE2, ANXA3/ZDHHC19, ANXA3/SLC51A, ANXA3/HPGD, ANXA3/SEMA6B, ANXA3/EFNA1, ANXA3/AGFG1, ANXA3/NSUN7, ANXA3/TNFAIP8L3, ANXA3/KREMEN1, ANXA3/ORM2, ANXA3/MIR646HG, ANXA3/KLF14, ARG1/PFKFB2, ARG1/MLLT1, ARG1/ANXA3, ARG1/GPR84, ARG1/OLAH, ARG1/ADAMTS3, ARG1/PCOLCE2, ARG1/ZDHHC19, ARG1/SLC51A, ARG1/HPGD, ARG1/SEMA6B, ARG1/EFNA1, ARG1/AGFG1, ARG1/NSUN7, ARG1/TNFAIP8L3, ARG1/KREMEN1, ARG1/ORM2, ARG1/MIR646HG, ARG1/KLF14, ATP9A/EPB41L4B, ATP9A/IL1R1, ATP9A/GADD45A, ATP9A/ARG1, ATP9A/PFKFB2, ATP9A/MLLT1, ATP9A/ANXA3, ATP9A/GPR84, ATP9A/OLAH, ATP9A/ADAMTS3, ATP9A/PCOLCE2, ATP9A/ZDHHC19, ATP9A/SLC51A, ATP9A/HPGD, ATP9A/SEMA6B, ATP9A/EFNA1, ATP9A/AGFG1, ATP9A/NSUN7, ATP9A/TNFAIP8L3, ATP9A/KREMEN1, ATP9A/ORM2, ATP9A/MIR646HG, ATP9A/KLF14, EFNA1/AGFG1, EFNA1/NSUN7, EFNA1/TNFAIP8L3, EFNA1/KREMEN1, EFNA1/ORM2, EFNA1/MIR646HG, EFNA1/KLF14, EPB41L4B/IL1R1, EPB41L4B/GADD45A, EPB41L4B/ARG1, EPB41L4B/PFKFB2, EPB41L4B/MLLT1, EPB41L4B/ANXA3, EPB41L4B/GPR84, EPB41L4B/OLAH,

EPB41L4B/ADAMTS3, EPB41L4B/PCOLCE2, EPB41L4B/ZDHHC19,
 EPB41L4B/SLC51A, EPB41L4B/HPGD, EPB41L4B/SEMA6B, EPB41L4B/EFNA1,
 EPB41L4B/AGFG1, EPB41L4B/NSUN7, EPB41L4B/TNFAIP8L3,
 EPB41L4B/KREMEN1, EPB41L4B/MIR646HG, EPB41L4B/KLF14, GADD45A/ARG1,
 GADD45A/PFKFB2, GADD45A/MLLT1, GADD45A/ANXA3, GADD45A/GPR84,
 GADD45A/OLAH, GADD45A/ADAMTS3, GADD45A/PCOLCE2,
 GADD45A/ZDHHC19, GADD45A/SLC51A, GADD45A/HPGD, GADD45A/SEMA6B,
 GADD45A/EFNA1, GADD45A/AGFG1, GADD45A/NSUN7, GADD45A/TNFAIP8L3,
 GADD45A/KREMEN1, GADD45A/ORM2, GADD45A/MIR646HG, GADD45A/KLF14,
 GPR84/OLAH, GPR84/ADAMTS3, GPR84/PCOLCE2, GPR84/ZDHHC19,
 GPR84/SLC51A, GPR84/HPGD, GPR84/SEMA6B, GPR84/EFNA1, GPR84/AGFG1,
 GPR84/NSUN7, GPR84/TNFAIP8L3, GPR84/KREMEN1, GPR84/ORM2,
 GPR84/MIR646HG, GPR84/KLF14, HPGD/SEMA6B, HPGD/EFNA1, HPGD/AGFG1,
 HPGD/NSUN7, HPGD/TNFAIP8L3, HPGD/KREMEN1, HPGD/ORM2,
 HPGD/MIR646HG, HPGD/KLF14, IL1R1/GADD45A, IL1R1/ARG1, IL1R1/PFKFB2,
 IL1R1/MLLT1, IL1R1/ANXA3, IL1R1/GPR84, IL1R1/OLAH, IL1R1/ADAMTS3,
 IL1R1/PCOLCE2, IL1R1/ZDHHC19, IL1R1/SLC51A, IL1R1/HPGD, IL1R1/SEMA6B,
 IL1R1/EFNA1, IL1R1/AGFG1, IL1R1/NSUN7, IL1R1/TNFAIP8L3, IL1R1/KREMEN1,
 IL1R1/ORM2, IL1R1/MIR646HG, IL1R1/KLF14, KREMEN1/ORM2,
 KREMEN1/MIR646HG, KREMEN1/KLF14, MIR646HG/KLF14, MLLT1/ANXA3,
 MLLT1/GPR84, MLLT1/OLAH, MLLT1/ADAMTS3, MLLT1/PCOLCE2,
 MLLT1/ZDHHC19, MLLT1/SLC51A, MLLT1/HPGD, MLLT1/SEMA6B,
 MLLT1/EFNA1, MLLT1/AGFG1, MLLT1/NSUN7, MLLT1/TNFAIP8L3,
 MLLT1/KREMEN1, MLLT1/ORM2, MLLT1/MIR646HG, MLLT1/KLF14,
 NSUN7/TNFAIP8L3, NSUN7/KREMEN1, NSUN7/ORM2, NSUN7/MIR646HG,
 NSUN7/KLF14, OLAH/ADAMTS3, OLAH/PCOLCE2, OLAH/ZDHHC19,
 OLAH/SLC51A, OLAH/HPGD, OLAH/SEMA6B, OLAH/EFNA1, OLAH/AGFG1,
 OLAH/NSUN7, OLAH/TNFAIP8L3, OLAH/KREMEN1, OLAH/ORM2,
 OLAH/MIR646HG, OLAH/KLF14, ORM2/MIR646HG, ORM2/KLF14,
 PCOLCE2/ZDHHC19, PCOLCE2/SLC51A, PCOLCE2/HPGD, PCOLCE2/SEMA6B,
 PCOLCE2/EFNA1, PCOLCE2/AGFG1, PCOLCE2/NSUN7, PCOLCE2/TNFAIP8L3,
 PCOLCE2/KREMEN1, PCOLCE2/ORM2, PCOLCE2/MIR646HG, PCOLCE2/KLF14,
 PFKFB2/MLLT1, PFKFB2/ANXA3, PFKFB2/GPR84, PFKFB2/OLAH,

PFKFB2/ADAMTS3, PFKFB2/PCOLCE2, PFKFB2/ZDHHC19, PFKFB2/SLC51A,
 PFKFB2/HPGD, PFKFB2/SEMA6B, PFKFB2/EFNA1, PFKFB2/AGFG1,
 PFKFB2/NSUN7, PFKFB2/TNFAIP8L3, PFKFB2/KREMEN1, PFKFB2/ORM2,
 PFKFB2/MIR646HG, PFKFB2/KLF14, SEMA6B/EFNA1, SEMA6B/AGFG1,
 SEMA6B/NSUN7, SEMA6B/TNFAIP8L3, SEMA6B/KREMEN1, SEMA6B/ORM2,
 SEMA6B/MIR646HG, SEMA6B/KLF14, SLC51A/HPGD, SLC51A/SEMA6B,
 SLC51A/EFNA1, SLC51A/AGFG1, SLC51A/NSUN7, SLC51A/TNFAIP8L3,
 SLC51A/KREMEN1, SLC51A/ORM2, SLC51A/MIR646HG, SLC51A/KLF14,
 TNFAIP8L3/KREMEN1, TNFAIP8L3/ORM2, TNFAIP8L3/MIR646HG,
 TNFAIP8L3/KLF14, ZDHHC19/SLC51A, ZDHHC19/HPGD, ZDHHC19/SEMA6B,
 ZDHHC19/EFNA1, ZDHHC19/AGFG1, ZDHHC19/NSUN7, ZDHHC19/TNFAIP8L3,
 ZDHHC19/KREMEN1, ZDHHC19/ORM2, ZDHHC19/MIR646HG, and
 ZDHHC19/KLF14; wherein the INF endotype signature pair is selected from: FECH/TFEC,
 TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A,
 ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A,
 RHCE/FECH, TFEC/CA1, SPTA1/FECH, ANKRD22/GLRX5, ANKRD22/GYP A,
 ANKRD22/IFIT1B, ANKRD22/ITLN1, ANKRD22/KLHDC8A, ANKRD22/RHCE,
 ANKRD22/RNF182, ANKRD22/SPTA1, ANKRD22/THEM5, ANKRD22/TSPAN5,
 APOL4/BNIP3L, APOL4/CA1, APOL4/DYRK3, APOL4/FAM83A, APOL4/GLRX5,
 APOL4/GYP A, APOL4/IFIT1B, APOL4/ITLN1, APOL4/KLHDC8A, APOL4/RHAG,
 APOL4/RHCE, APOL4/RIOK3, APOL4/RNF182, APOL4/SPTA1, APOL4/THEM5,
 APOL4/TLCD4, APOL4/TMCC2, APOL4/TSPAN5, APOL4/TSP02, BNIP3L/ANKRD22,
 BNIP3L/CA1, BNIP3L/CARD17, BNIP3L/CD274, BNIP3L/DYRK3, BNIP3L/FAM83A,
 BNIP3L/GBP5, BNIP3L/GLRX5, BNIP3L/GYP A, BNIP3L/IFIT1B, BNIP3L/ITLN1,
 BNIP3L/KLHDC8A, BNIP3L/P2RY14, BNIP3L/RHAG, BNIP3L/RHCE,
 BNIP3L/RNF182, BNIP3L/SPTA1, BNIP3L/TFEC, BNIP3L/THEM5, BNIP3L/TLCD4,
 BNIP3L/TMCC2, BNIP3L/TSPAN5, BNIP3L/TSP02, CA1/ANKRD22, CA1/CARD17,
 CA1/DYRK3, CA1/FAM83A, CA1/GBP5, CA1/GLRX5, CA1/GYP A, CA1/IFIT1B,
 CA1/ITLN1, CA1/KLHDC8A, CA1/P2RY14, CA1/RHCE, CA1/RNF182, CA1/SPTA1,
 CA1/THEM5, CA1/TLCD4, CA1/TSPAN5, CD274/CA1, CD274/DYRK3,
 CD274/FAM83A, CD274/GLRX5, CD274/GYP A, CD274/IFIT1B, CD274/ITLN1,
 CD274/KLHDC8A, CD274/RHCE, CD274/RNF182, CD274/SPTA1, CD274/THEM5,
 CD274/TLCD4, CD274/TMCC2, CD274/TSPAN5, DYRK3/ANKRD22,

DYRK3/CARD17, DYRK3/FAM83A, DYRK3/GBP5, DYRK3/GLRX5, DYRK3/GYP A,
 DYRK3/IFIT1B, DYRK3/ITLN1, DYRK3/KLHDC8A, DYRK3/P2RY14, DYRK3/RHCE,
 DYRK3/RNF182, DYRK3/SPTA1, DYRK3/THEM5, DYRK3/TLCD4, DYRK3/TSPAN5,
 FAM83A/ANKRD22, FAM83A/CARD17, FAM83A/GBP5, FAM83A/GLRX5,
 FAM83A/GYP A, FAM83A/IFIT1B, FAM83A/ITLN1, FAM83A/KLHDC8A,
 FAM83A/P2RY14, FAM83A/RHCE, FAM83A/RNF182, FAM83A/SPTA1,
 FAM83A/THEM5, FAM83A/TLCD4, FAM83A/TSPAN5, FECH/ANKRD22,
 FECH/APOL4, FECH/BNIP3L, FECH/CA1, FECH/CARD17, FECH/CD274,
 FECH/DYRK3, FECH/FAM83A, FECH/GBP5, FECH/GLRX5, FECH/GYP A,
 FECH/IFIT1B, FECH/ITLN1, FECH/KLHDC8A, FECH/P2RY14, FECH/RHAG,
 FECH/RHCE, FECH/RIOK3, FECH/RNF182, FECH/SPTA1, FECH/TFEC,
 FECH/THEM5, FECH/TLCD4, FECH/TMCC2, FECH/TSPAN5, FECH/TSPO2,
 GBP5/GLRX5, GBP5/GYP A, GBP5/IFIT1B, GBP5/ITLN1, GBP5/KLHDC8A,
 GBP5/RHCE, GBP5/RNF182, GBP5/SPTA1, GBP5/THEM5, GBP5/TSPAN5,
 GLRX5/CARD17, GLRX5/IFIT1B, GLRX5/RHCE, GLRX5/THEM5, GYP A/CARD17,
 GYP A/GLRX5, GYP A/IFIT1B, GYP A/ITLN1, GYP A/P2RY14, GYP A/RHCE,
 GYP A/RNF182, GYP A/THEM5, IFIT1B/CARD17, ITLN1/CARD17, ITLN1/GLRX5,
 ITLN1/IFIT1B, ITLN1/RHCE, ITLN1/RNF182, ITLN1/THEM5, KLHDC8A/CARD17,
 KLHDC8A/GLRX5, KLHDC8A/GYP A, KLHDC8A/IFIT1B, KLHDC8A/ITLN1,
 KLHDC8A/P2RY14, KLHDC8A/RHCE, KLHDC8A/RNF182, KLHDC8A/SPTA1,
 KLHDC8A/THEM5, KLHDC8A/TSPAN5, P2RY14/GLRX5, P2RY14/IFIT1B,
 P2RY14/ITLN1, P2RY14/RHCE, P2RY14/RNF182, P2RY14/THEM5, RHAG/ANKRD22,
 RHAG/CA1, RHAG/CARD17, RHAG/CD274, RHAG/DYRK3, RHAG/FAM83A,
 RHAG/GBP5, RHAG/GLRX5, RHAG/GYP A, RHAG/IFIT1B, RHAG/ITLN1,
 RHAG/KLHDC8A, RHAG/P2RY14, RHAG/RHCE, RHAG/RNF182, RHAG/SPTA1,
 RHAG/THEM5, RHAG/TLCD4, RHAG/TMCC2, RHAG/TSPAN5, RHAG/TSPO2,
 RHCE/CARD17, RHCE/IFIT1B, RHCE/THEM5, RIOK3/ANKRD22, RIOK3/BNIP3L,
 RIOK3/CA1, RIOK3/CARD17, RIOK3/CD274, RIOK3/DYRK3, RIOK3/FAM83A,
 RIOK3/GBP5, RIOK3/GLRX5, RIOK3/GYP A, RIOK3/IFIT1B, RIOK3/ITLN1,
 RIOK3/KLHDC8A, RIOK3/P2RY14, RIOK3/RHAG, RIOK3/RHCE, RIOK3/RNF182,
 RIOK3/SPTA1, RIOK3/TFEC, RIOK3/THEM5, RIOK3/TLCD4, RIOK3/TMCC2,
 RIOK3/TSPAN5, RIOK3/TSPO2, RNF182/CARD17, RNF182/GLRX5, RNF182/IFIT1B,
 RNF182/RHCE, RNF182/THEM5, SPTA1/CARD17, SPTA1/GLRX5, SPTA1/GYP A,

SPTA1/IFIT1B, SPTA1/ITLN1, SPTA1/P2RY14, SPTA1/RHCE, SPTA1/RNF182, SPTA1/THEM5, SPTA1/TSPAN5, TFEC/CA1, TFEC/DYRK3, TFEC/FAM83A, TFEC/GLRX5, TFEC/GYP A, TFEC/IFIT1B, TFEC/ITLN1, TFEC/KLHDC8A, TFEC/RHAG, TFEC/RHCE, TFEC/RNF182, TFEC/SPTA1, TFEC/THEM5, TFEC/TLCD4, TFEC/TMCC2, TFEC/TSPAN5, TFEC/TSP02, THEM5/CARD17, THEM5/IFIT1B, TLCD4/ANKRD22, TLCD4/CARD17, TLCD4/GBP5, TLCD4/GLRX5, TLCD4/GYP A, TLCD4/IFIT1B, TLCD4/ITLN1, TLCD4/KLHDC8A, TLCD4/P2RY14, TLCD4/RHCE, TLCD4/RNF182, TLCD4/SPTA1, TLCD4/THEM5, TLCD4/TSPAN5, TMCC2/ANKRD22, TMCC2/CA1, TMCC2/CARD17, TMCC2/DYRK3, TMCC2/FAM83A, TMCC2/GBP5, TMCC2/GLRX5, TMCC2/GYP A, TMCC2/IFIT1B, TMCC2/ITLN1, TMCC2/KLHDC8A, TMCC2/P2RY14, TMCC2/RHCE, TMCC2/RNF182, TMCC2/SPTA1, TMCC2/THEM5, TMCC2/TLCD4, TMCC2/TSPAN5, TSPAN5/CARD17, TSPAN5/GLRX5, TSPAN5/GYP A, TSPAN5/IFIT1B, TSPAN5/ITLN1, TSPAN5/P2RY14, TSPAN5/RHCE, TSPAN5/RNF182, TSPAN5/THEM5, TSP02/ANKRD22, TSP02/CA1, TSP02/CARD17, TSP02/CD274, TSP02/DYRK3, TSP02/FAM83A, TSP02/GBP5, TSP02/GLRX5, TSP02/GYP A, TSP02/IFIT1B, TSP02/ITLN1, TSP02/KLHDC8A, TSP02/P2RY14, TSP02/RHCE, TSP02/RNF182, TSP02/SPTA1, TSP02/THEM5, TSP02/TLCD4, TSP02/TMCC2, and TSP02/TSPAN5; wherein the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1, ADAM23/GPR34, ADAM23/MAP7, ADAM23/PLCB1, ADAM23/SPRED1, ALOX15/GPR34, ALOX15/PLCB1, ALOX15/SPRED1, BAALC/GPR34, BAALC/PLCB1, BAALC/SPRED1, CACNA2D3/DYNC2H1, CACNA2D3/GPR34, CACNA2D3/PLCB1, CACNA2D3/SPRED1, CACNA2D3/ZNF600, GPR34/DYNC2H1, GPR34/GRAMD1C, GPR34/PLCB1, GPR34/TPRG1, GPR34/ZNF600, GPR82/DYNC2H1, GPR82/GPR34, GPR82/GRAMD1C, GPR82/PLCB1, GPR82/TPRG1, GPR82/ZNF600, GRAMD1C/DYNC2H1, GRAMD1C/PLCB1, GRAMD1C/ZNF600, HRK/DYNC2H1, HRK/GPR34, HRK/MAP7, HRK/PLCB1, HRK/SPRED1, HRK/ZNF600, IL5RA/DYNC2H1, IL5RA/GPR34, IL5RA/PLCB1, IL5RA/SPRED1, IL5RA/TRIM2, MAP7/BAALC, MAP7/CACNA2D3, MAP7/DYNC2H1, MAP7/GPR34, MAP7/GPR82,

MAP7/GRAMD1C, MAP7/PLCB1, MAP7/SPRED1, MAP7/TPRG1, MAP7/ZNF600, PLCB1/DYNC2H1, PLCB1/TPRG1, PLCB1/ZNF600, PRSS33/GPR34, PRSS33/PLCB1, PRSS33/SPRED1, SDC2/DYNC2H1, SDC2/GPR34, SDC2/PLCB1, SDC2/ZNF600, SIGLEC8/DYNC2H1, SIGLEC8/GPR34, SIGLEC8/MAP7, SIGLEC8/PLCB1, SIGLEC8/SPRED1, SIGLEC8/TRIM2, SMPD3/DYNC2H1, SMPD3/GPR34, SMPD3/MAP7, SMPD3/PLCB1, SMPD3/SPRED1, SMPD3/TRIM2, SPRED1/DYNC2H1, SPRED1/GPR34, SPRED1/GPR82, SPRED1/GRAMD1C, SPRED1/PLCB1, SPRED1/SDC2, SPRED1/TPRG1, SPRED1/ZNF600, TRIM2/CACNA2D3, TRIM2/DYNC2H1, TRIM2/GPR34, TRIM2/GPR82, TRIM2/GRAMD1C, TRIM2/HRK, TRIM2/MAP7, TRIM2/PLCB1, TRIM2/SDC2, TRIM2/SPRED1, TRIM2/TPRG1, and TRIM2/ZNF600; wherein the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1, APOL1/BATF2, APOL1/CLEC4F, APOL1/EPSTI1, APOL1/EXOC3L1, APOL1/HES4, APOL1/IFITM3, APOL1/LY6E, APOL1/RSAD2, APOL1/SEPTIN4, APOL1/SERPING1, APOL1/TPPP3, BATF2/EXOC3L1, BATF2/HES4, CLEC4F/BATF2, CLEC4F/EXOC3L1, EPSTI1/BATF2, EPSTI1/CLEC4F, EPSTI1/EXOC3L1, EPSTI1/HES4, EPSTI1/IFITM3, EPSTI1/LY6E, EPSTI1/RSAD2, EPSTI1/SERPING1, EPSTI1/TPPP3, ETV7/APOL1, ETV7/BATF2, ETV7/CLEC4F, ETV7/EPSTI1, ETV7/EXOC3L1, ETV7/HES4, ETV7/IFITM3, ETV7/LAMP3, ETV7/LY6E, ETV7/PLEKHO1, ETV7/RSAD2, ETV7/SEPTIN4, ETV7/SERPING1, ETV7/TPPP3, EXOC3L1/HES4, IFITM3/SERPING1, IFITM3/CLEC4F, IFITM3/TPPP3, IFITM3/LY6E, IFITM3/EXOC3L1, IFITM3/HES4, LAMP3/APOL1, LAMP3/BATF2, LAMP3/CLEC4F, LAMP3/EPSTI1, LAMP3/EXOC3L1, LAMP3/HES4, LAMP3/IFITM3, LAMP3/LY6E, LAMP3/RSAD2, LAMP3/SEPTIN4, LAMP3/SERPING1, LAMP3/TPPP3, LY6E/BATF2, LY6E/EXOC3L1, PLEKHO1/APOL1, PLEKHO1/BATF2, PLEKHO1/EPSTI1, PLEKHO1/EXOC3L1, PLEKHO1/IFITM3, PLEKHO1/LAMP3, PLEKHO1/RSAD2, PLEKHO1/SEPTIN4, PLEKHO1/SERPING1, RSAD2/BATF2, RSAD2/CLEC4F, RSAD2/EXOC3L1, RSAD2/HES4, RSAD2/IFITM3, RSAD2/LY6E, RSAD2/SERPING1, RSAD2/TPPP3, SEPTIN4/BATF2, SEPTIN4/CLEC4F, SEPTIN4/EPSTI1, SEPTIN4/EXOC3L1, SEPTIN4/HES4, SEPTIN4/IFITM3, SEPTIN4/LY6E, SEPTIN4/RSAD2, SEPTIN4/SERPING1, SEPTIN4/TPPP3, SERPING1/BATF2, SERPING1/CLEC4F,

SERPING1/EXOC3L1, SERPING1/HES4, SERPING1/LY6E, SERPING1/TPPP3, TPPP3/BATF2, and TPPP3/EXOC3L1; and wherein the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL, CAV1/LGALS3BP, CAV1/OTOF, CDC45/LGALS3BP, CDC45/OTOF, CENPF/KCTD14, GPRC5D/OTOF, GTSE1/LGALS3BP, GTSE1/OTOF, IGF1/LGALS3BP, IGF1/OTOF, KCTD14/KLHL14, KCTD14/PDIA4, KCTD14/TSHR, KIF14/KCTD14, LGALS3BP/CENPF, LGALS3BP/GPRC5D, LGALS3BP/IFI27, LGALS3BP/IGLL5, LGALS3BP/KCTD14, LGALS3BP/KIF14, LGALS3BP/KIF15, LGALS3BP/KLHL14, LGALS3BP/MIR155HG, LGALS3BP/MIXL1, LGALS3BP/OTOF, LGALS3BP/PDIA4, LGALS3BP/PLAAT2, LGALS3BP/SDC1, LGALS3BP/SLC16A14, LGALS3BP/TSHR, OTOF/CENPF, OTOF/IFI27, OTOF/IGLL5, OTOF/KCTD14, OTOF/KIF14, OTOF/KIF15, OTOF/KLHL14, OTOF/MIR155HG, OTOF/MIXL1, OTOF/PDIA4, OTOF/PLAAT2, OTOF/SDC1, OTOF/SLC16A14, OTOF/TSHR, PLAAT2/KCTD14, TNFRSF17/LGALS3BP, and TNFRSF17/OTOF. It will be appreciated by a person skilled in the art that embodiments for such methods for classifying a subject into a sepsis mechanistic endotype in such methods of treatment and uses can be varied as described herein for the methods for classifying a subject into a sepsis mechanistic endotype.

[00112] The one or more therapies that act specifically against a mechanism associated with the sepsis mechanistic endotype are any suitable therapies that act specifically against a mechanism associated with the particular sepsis mechanistic endotype, the selection of which can be readily made by a person skilled in the art having regard to the present disclosure.

[00113] For example, a person skilled in the art would readily appreciate that stimulating part of the immune system that is lacking in patients with the NPS endotype may be useful to treat subjects classified as having the NPS endotype. In an embodiment, the treatment of subjects classified as having the NPS endotype comprises a treatment that reverses cellular reprogramming and/or boosts T-cell function. In another embodiment, the treatment that reverses cellular reprogramming is interferon gamma (IFN- γ).

[00114] A person skilled in the art would also readily appreciate that because the INF endotype is inflammatory, an anti-inflammatory therapy may be useful to treat subjects classified as having

the INF endotype whereas this would not be indicated, for example, for subjects classified as having the NPS endotype, which demonstrates an early immunosuppressive character. In an embodiment, the treatment of subjects classified as having the INF endotype comprises treatment with an anti-inflammatory therapy. In another embodiment, the anti-inflammatory therapy is a glucocorticoid or a monoclonal antibody against TNF- α .

[00115] A person skilled in the art would also readily appreciate that because the IHD and ADA endotypes demonstrate neutropenia, treatment with one or more therapies useful for treating neutropenia, such as granulocyte macrophage colony-stimulating factor (GM-CSF) therapy may be useful in treating subjects classified as having the IHD and/or ADA endotypes. In an embodiment, the treatment of subjects classified as having the IHD or ADA endotypes comprises treatment with a therapy useful for treating neutropenia. In another embodiment, the therapy useful for treating neutropenia is granulocyte macrophage colony-stimulating factor (GM-CSF).

[00116] A person skilled in the art would also readily appreciate that because the INF and IHD endotypes demonstrate turn on of reactive oxygen species (ROS) production, anti-oxidant therapy may be useful in treating subjects classified as having the INF and/or IHD endotypes. In an embodiment, the treatment of subjects classified as having the INF or IHD endotypes comprises treatment with anti-oxidant therapy.

[00117] Given the repercussions of increased antibiotic resistance and health care costs, triaging sepsis patients prior to treatment with antibiotics may also be desirable.

[00118] Accordingly, the present disclosure also includes a method of treating sepsis in a subject predicted as having high or intermediate severity sepsis, the method comprising: (a) predicting that the subject has high or intermediate severity sepsis by a method comprising: (i) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (ii) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, and intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5; and wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F,

CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19; and (b) administering an effective amount of one or more antibiotics to the subject. The present disclosure also includes a use of an effective amount of one or more antibiotics for treatment of sepsis in a subject predicted as having high or intermediate severity sepsis by a method comprising: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, and intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5; and wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9,

PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19. The present disclosure also includes a use of an effective amount of one or more antibiotics for preparation of a medicament for treatment of sepsis in a subject predicted as having high or intermediate severity sepsis by a method comprising: (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (b) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, and intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5; and wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19. The present disclosure further includes one or more antibiotics for use to treat sepsis in a subject predicted as having

high or intermediate severity sepsis by a method for predicting severity of sepsis comprising: (i) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and (ii) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, and intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5; and wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19. In an embodiment, the sepsis is high severity sepsis. In another embodiment of the present disclosure, the sepsis is intermediate severity sepsis. It will be appreciated by a person skilled in the art that embodiments of such a method for predicting that the subject has high or intermediate severity sepsis can be varied, as appropriate, as described herein for the embodiments of the method for predicting severity of sepsis in a subject, wherein the severity of the sepsis is selected from high severity sepsis, intermediate severity sepsis and low severity sepsis.

[00119] Examples of suitable antibiotics for treating sepsis include, but are not limited to, glycopeptides (such as vancomycin, oritavancin or telavancin) cephalosporins (such as ceftriaxone, cefotaxime, or cefepime), beta-lactams/beta-lactamase inhibitors (such as

piperacillin-tazobactam, or ticarcillin-clavulanate), carbapenems (such as imipenem or meropenem), quinolones and fluoroquinolones (such as ciprofloxacin, moxifloxacin or levofloxacin), aminoglycosides (such as gentamicin, tobramycin or amikacin), macrolides (such as azithromycin, clarithromycin or erythromycin) and monobactams (such as aztreonam), and various combinations thereof. Typically, combinations comprise antibiotics from different classes. In an embodiment, the one or more antibiotics is one or a combination of a glycopeptide, a cephalosporin, a beta-lactam, a beta-lactamase inhibitor, a carbapenem, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide and a monobactam.

[00120] The one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics can be administered to a subject or used in a variety of forms depending on the selected route of administration or use, as will be understood by those skilled in the art, and which may depend, for example, on the particular therapy, antibiotic or combination thereof. In an embodiment, the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics are administered to the subject, or used, by oral (including buccal) or parenteral (including intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, topical, patch, pump and transdermal) administration or use and the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics formulated accordingly. For example, the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics are administered or used in an injection, in a spray, in a tablet/caplet, in a powder, topically, in a gel, in drops, by a patch, by an implant, by a slow release pump or by any other suitable method of administration or use, the selection of which can be made by a person skilled in the art.

[00121] Treatment methods or uses comprise administering to a subject or use of an effective amount of one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics, as the case may be, optionally consisting of a single administration or use, or alternatively comprising a series of administrations or uses. The length of the treatment period or use depends on a variety of factors, such as the severity of the sepsis, the age of the subject, the identity of the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics, and/or a combination thereof. It will also be appreciated

that the effective amount of a therapy, antibiotic or combination thereof used for the treatment or use may increase or decrease over the course of a particular treatment regime or use. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In an embodiment, the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics, as the case may be, are administered or used in an amount and for duration sufficient to treat the subject.

[00122] The one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics may be administered or used alone or in combination (i.e., a combination of therapies or a combination of antibiotics, as the case may be). When administered or used in combination, it is an embodiment that the combination of therapies or combination of antibiotics, as the case may be, are administered or used contemporaneously. As used herein the term “contemporaneous” in reference to administration of two substances to a subject or use means providing each of the two substances so that they are both biologically active in the individual at the same time. The exact details of the administration or use will depend on the pharmacokinetics of the two substances in the presence of each other, and can include administering or using the two substances within a few hours of each other, or even administering or using one substance within 24 hours of administration or use of the other, if the pharmacokinetics are suitable. Design of suitable dosing regimens is routine for one skilled in the art. In particular embodiments, two substances will be administered or used substantially simultaneously, i.e., within minutes of each other, or in a single composition that contains both substances. It is a further embodiment that a combination of the two substances is administered to a subject or used in a non-contemporaneous fashion.

[00123] The dosage of the one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype or one or more antibiotics can vary depending on many factors such as pharmacodynamic properties, the mode of administration or use, the age, health and weight of the subject, the frequency of the treatment or use and the type of concurrent treatment or use, if any, and the clearance rate in the subject. One of skill in the art can determine the appropriate dosage for a particular therapy, antibiotic or combination thereof.

III. Further Aspects and Embodiments

[00124] The present disclosure also includes a method for identifying a candidate agent for the treatment of sepsis in a subject classified as having a sepsis mechanistic endotype selected

from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising: (a) contacting a cell having the sepsis endotype with a test agent, (b) determining the level of expression for each of a plurality of genes in the cell to provide an expression signature; (c) comparing the expression signature with a reference signature, wherein the reference signature represents the level of expression of the plurality of genes in a normal cell; and (d) selecting the test agent as a candidate agent for treatment of the sepsis when the expression signature substantially corresponds with the reference signature, wherein the expression signature and reference signature comprise an NPS endotype sub-signature for an NPS endotype cell, an INF endotype sub-signature for an INF endotype cell, an IHD endotype sub-signature for an IHD endotype cell, an IFN endotype sub-signature for an IFN endotype cell and an ADA endotype sub-signature for an ADA endotype cell, wherein the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, and XCR1; wherein the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYPA, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175,

RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC4A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, and YPEL4; wherein the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, and TRIM2; wherein the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, and LAMP3; and wherein the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, USP18, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, and TTC21A.

[00125] The present disclosure also includes a method for identifying a candidate agent for the treatment of sepsis in a subject classified as having a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising: (a) contacting a cell having the sepsis endotype with a test agent, (b) determining the level of expression for each of a plurality of genes in the cell to provide an expression signature; (c) comparing the expression signature with a reference signature, wherein the reference signature represents the level of expression of the plurality of genes in a normal cell; and (d) selecting the test agent as a candidate agent for treatment of the sepsis when the expression signature substantially corresponds with the reference signature, wherein the expression signature and reference signature comprise an NPS endotype signature pair for an NPS endotype cell, an INF endotype signature pair for an INF endotype cell, an IHD endotype signature pair for an IHD endotype cell, an IFN endotype signature pair for an IFN endotype cell, and an ADA endotype signature pair for an ADA endotype cell, wherein the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1,

EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, MLLT1/KLF14, ADAMTS3/PCOLCE2, ADAMTS3/ZDHHC19, ADAMTS3/SLC51A, ADAMTS3/HPGD, ADAMTS3/SEMA6B, ADAMTS3/EFNA1, ADAMTS3/AGFG1, ADAMTS3/NSUN7, ADAMTS3/TNFAIP8L3, ADAMTS3/KREMEN1, ADAMTS3/ORM2, ADAMTS3/MIR646HG, ADAMTS3/KLF14, AGFG1/NSUN7, AGFG1/TNFAIP8L3, AGFG1/KREMEN1, AGFG1/ORM2, AGFG1/MIR646HG, AGFG1/KLF14, ANXA3/GPR84, ANXA3/OLAH, ANXA3/ADAMTS3, ANXA3/PCOLCE2, ANXA3/ZDHHC19, ANXA3/SLC51A, ANXA3/HPGD, ANXA3/SEMA6B, ANXA3/EFNA1, ANXA3/AGFG1, ANXA3/NSUN7, ANXA3/TNFAIP8L3, ANXA3/KREMEN1, ANXA3/ORM2, ANXA3/MIR646HG, ANXA3/KLF14, ARG1/PFKFB2, ARG1/MLLT1, ARG1/ANXA3, ARG1/GPR84, ARG1/OLAH, ARG1/ADAMTS3, ARG1/PCOLCE2, ARG1/ZDHHC19, ARG1/SLC51A, ARG1/HPGD, ARG1/SEMA6B, ARG1/EFNA1, ARG1/AGFG1, ARG1/NSUN7, ARG1/TNFAIP8L3, ARG1/KREMEN1, ARG1/ORM2, ARG1/MIR646HG, ARG1/KLF14, ATP9A/EPB41L4B, ATP9A/IL1R1, ATP9A/GADD45A, ATP9A/ARG1, ATP9A/PFKFB2, ATP9A/MLLT1, ATP9A/ANXA3, ATP9A/GPR84, ATP9A/OLAH, ATP9A/ADAMTS3, ATP9A/PCOLCE2, ATP9A/ZDHHC19, ATP9A/SLC51A, ATP9A/HPGD, ATP9A/SEMA6B, ATP9A/EFNA1, ATP9A/AGFG1, ATP9A/NSUN7, ATP9A/TNFAIP8L3, ATP9A/KREMEN1, ATP9A/ORM2, ATP9A/MIR646HG, ATP9A/KLF14, EFNA1/AGFG1, EFNA1/NSUN7, EFNA1/TNFAIP8L3, EFNA1/KREMEN1, EFNA1/ORM2, EFNA1/MIR646HG, EFNA1/KLF14, EPB41L4B/IL1R1, EPB41L4B/GADD45A, EPB41L4B/ARG1, EPB41L4B/PFKFB2, EPB41L4B/MLLT1, EPB41L4B/ANXA3, EPB41L4B/GPR84, EPB41L4B/OLAH, EPB41L4B/ADAMTS3, EPB41L4B/PCOLCE2, EPB41L4B/ZDHHC19, EPB41L4B/SLC51A, EPB41L4B/HPGD, EPB41L4B/SEMA6B, EPB41L4B/EFNA1, EPB41L4B/AGFG1, EPB41L4B/NSUN7, EPB41L4B/TNFAIP8L3, EPB41L4B/KREMEN1, EPB41L4B/MIR646HG, EPB41L4B/KLF14, GADD45A/ARG1, GADD45A/PFKFB2, GADD45A/MLLT1, GADD45A/ANXA3, GADD45A/GPR84, GADD45A/OLAH, GADD45A/ADAMTS3, GADD45A/PCOLCE2, GADD45A/ZDHHC19, GADD45A/SLC51A, GADD45A/HPGD, GADD45A/SEMA6B, GADD45A/EFNA1, GADD45A/AGFG1, GADD45A/NSUN7, GADD45A/TNFAIP8L3, GADD45A/KREMEN1, GADD45A/ORM2, GADD45A/MIR646HG, GADD45A/KLF14, GPR84/OLAH, GPR84/ADAMTS3, GPR84/PCOLCE2, GPR84/ZDHHC19, GPR84/SLC51A, GPR84/HPGD, GPR84/SEMA6B, GPR84/EFNA1, GPR84/AGFG1, GPR84/NSUN7,

GPR84/TNFAIP8L3, GPR84/KREMEN1, GPR84/ORM2, GPR84/MIR646HG, GPR84/KLF14, HPGD/SEMA6B, HPGD/EFNA1, HPGD/AGFG1, HPGD/NSUN7, HPGD/TNFAIP8L3, HPGD/KREMEN1, HPGD/ORM2, HPGD/MIR646HG, HPGD/KLF14, IL1R1/GADD45A, IL1R1/ARG1, IL1R1/PFKFB2, IL1R1/MLLT1, IL1R1/ANXA3, IL1R1/GPR84, IL1R1/OLAH, IL1R1/ADAMTS3, IL1R1/PCOLCE2, IL1R1/ZDHHC19, IL1R1/SLC51A, IL1R1/HPGD, IL1R1/SEMA6B, IL1R1/EFNA1, IL1R1/AGFG1, IL1R1/NSUN7, IL1R1/TNFAIP8L3, IL1R1/KREMEN1, IL1R1/ORM2, IL1R1/MIR646HG, IL1R1/KLF14, KREMEN1/ORM2, KREMEN1/MIR646HG, KREMEN1/KLF14, MIR646HG/KLF14, MLLT1/ANXA3, MLLT1/GPR84, MLLT1/OLAH, MLLT1/ADAMTS3, MLLT1/PCOLCE2, MLLT1/ZDHHC19, MLLT1/SLC51A, MLLT1/HPGD, MLLT1/SEMA6B, MLLT1/EFNA1, MLLT1/AGFG1, MLLT1/NSUN7, MLLT1/TNFAIP8L3, MLLT1/KREMEN1, MLLT1/ORM2, MLLT1/MIR646HG, MLLT1/KLF14, NSUN7/TNFAIP8L3, NSUN7/KREMEN1, NSUN7/ORM2, NSUN7/MIR646HG, NSUN7/KLF14, OLAH/ADAMTS3, OLAH/PCOLCE2, OLAH/ZDHHC19, OLAH/SLC51A, OLAH/HPGD, OLAH/SEMA6B, OLAH/EFNA1, OLAH/AGFG1, OLAH/NSUN7, OLAH/TNFAIP8L3, OLAH/KREMEN1, OLAH/ORM2, OLAH/MIR646HG, OLAH/KLF14, ORM2/MIR646HG, ORM2/KLF14, PCOLCE2/ZDHHC19, PCOLCE2/SLC51A, PCOLCE2/HPGD, PCOLCE2/SEMA6B, PCOLCE2/EFNA1, PCOLCE2/AGFG1, PCOLCE2/NSUN7, PCOLCE2/TNFAIP8L3, PCOLCE2/KREMEN1, PCOLCE2/ORM2, PCOLCE2/MIR646HG, PCOLCE2/KLF14, PFKFB2/MLLT1, PFKFB2/ANXA3, PFKFB2/GPR84, PFKFB2/OLAH, PFKFB2/ADAMTS3, PFKFB2/PCOLCE2, PFKFB2/ZDHHC19, PFKFB2/SLC51A, PFKFB2/HPGD, PFKFB2/SEMA6B, PFKFB2/EFNA1, PFKFB2/AGFG1, PFKFB2/NSUN7, PFKFB2/TNFAIP8L3, PFKFB2/KREMEN1, PFKFB2/ORM2, PFKFB2/MIR646HG, PFKFB2/KLF14, SEMA6B/EFNA1, SEMA6B/AGFG1, SEMA6B/NSUN7, SEMA6B/TNFAIP8L3, SEMA6B/KREMEN1, SEMA6B/ORM2, SEMA6B/MIR646HG, SEMA6B/KLF14, SLC51A/HPGD, SLC51A/SEMA6B, SLC51A/EFNA1, SLC51A/AGFG1, SLC51A/NSUN7, SLC51A/TNFAIP8L3, SLC51A/KREMEN1, SLC51A/ORM2, SLC51A/MIR646HG, SLC51A/KLF14, TNFAIP8L3/KREMEN1, TNFAIP8L3/ORM2, TNFAIP8L3/MIR646HG, TNFAIP8L3/KLF14, ZDHHC19/SLC51A, ZDHHC19/HPGD, ZDHHC19/SEMA6B, ZDHHC19/EFNA1, ZDHHC19/AGFG1, ZDHHC19/NSUN7, ZDHHC19/TNFAIP8L3, ZDHHC19/KREMEN1, ZDHHC19/ORM2, ZDHHC19/MIR646HG, and ZDHHC19/KLF14; wherein the INF endotype signature pair is

selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, SPTA1/FECH, ANKRD22/GLRX5, ANKRD22/GYP A, ANKRD22/IFIT1B, ANKRD22/ITLN1, ANKRD22/KLHDC8A, ANKRD22/RHCE, ANKRD22/RNF182, ANKRD22/SPTA1, ANKRD22/THEM5, ANKRD22/TSPAN5, APOL4/BNIP3L, APOL4/CA1, APOL4/DYRK3, APOL4/FAM83A, APOL4/GLRX5, APOL4/GYP A, APOL4/IFIT1B, APOL4/ITLN1, APOL4/KLHDC8A, APOL4/RHAG, APOL4/RHCE, APOL4/RIOK3, APOL4/RNF182, APOL4/SPTA1, APOL4/THEM5, APOL4/TLCD4, APOL4/TMCC2, APOL4/TSPAN5, APOL4/TSP02, BNIP3L/ANKRD22, BNIP3L/CA1, BNIP3L/CARD17, BNIP3L/CD274, BNIP3L/DYRK3, BNIP3L/FAM83A, BNIP3L/GBP5, BNIP3L/GLRX5, BNIP3L/GYP A, BNIP3L/IFIT1B, BNIP3L/ITLN1, BNIP3L/KLHDC8A, BNIP3L/P2RY14, BNIP3L/RHAG, BNIP3L/RHCE, BNIP3L/RNF182, BNIP3L/SPTA1, BNIP3L/TFEC, BNIP3L/THEM5, BNIP3L/TLCD4, BNIP3L/TMCC2, BNIP3L/TSPAN5, BNIP3L/TSP02, CA1/ANKRD22, CA1/CARD17, CA1/DYRK3, CA1/FAM83A, CA1/GBP5, CA1/GLRX5, CA1/GYP A, CA1/IFIT1B, CA1/ITLN1, CA1/KLHDC8A, CA1/P2RY14, CA1/RHCE, CA1/RNF182, CA1/SPTA1, CA1/THEM5, CA1/TLCD4, CA1/TSPAN5, CD274/CA1, CD274/DYRK3, CD274/FAM83A, CD274/GLRX5, CD274/GYP A, CD274/IFIT1B, CD274/ITLN1, CD274/KLHDC8A, CD274/RHCE, CD274/RNF182, CD274/SPTA1, CD274/THEM5, CD274/TLCD4, CD274/TMCC2, CD274/TSPAN5, DYRK3/ANKRD22, DYRK3/CARD17, DYRK3/FAM83A, DYRK3/GBP5, DYRK3/GLRX5, DYRK3/GYP A, DYRK3/IFIT1B, DYRK3/ITLN1, DYRK3/KLHDC8A, DYRK3/P2RY14, DYRK3/RHCE, DYRK3/RNF182, DYRK3/SPTA1, DYRK3/THEM5, DYRK3/TLCD4, DYRK3/TSPAN5, FAM83A/ANKRD22, FAM83A/CARD17, FAM83A/GBP5, FAM83A/GLRX5, FAM83A/GYP A, FAM83A/IFIT1B, FAM83A/ITLN1, FAM83A/KLHDC8A, FAM83A/P2RY14, FAM83A/RHCE, FAM83A/RNF182, FAM83A/SPTA1, FAM83A/THEM5, FAM83A/TLCD4, FAM83A/TSPAN5, FECH/ANKRD22, FECH/APOL4, FECH/BNIP3L, FECH/CA1, FECH/CARD17, FECH/CD274, FECH/DYRK3, FECH/FAM83A, FECH/GBP5, FECH/GLRX5, FECH/GYP A, FECH/IFIT1B, FECH/ITLN1, FECH/KLHDC8A, FECH/P2RY14, FECH/RHAG, FECH/RHCE, FECH/RIOK3, FECH/RNF182, FECH/SPTA1, FECH/TFEC, FECH/THEM5, FECH/TLCD4, FECH/TMCC2, FECH/TSPAN5, FECH/TSP02, GBP5/GLRX5, GBP5/GYP A, GBP5/IFIT1B, GBP5/ITLN1, GBP5/KLHDC8A, GBP5/RHCE,

GBP5/RNF182, GBP5/SPTA1, GBP5/THEM5, GBP5/TSPAN5, GLRX5/CARD17, GLRX5/IFIT1B, GLRX5/RHCE, GLRX5/THEM5, GYP A/CARD17, GYP A/GLRX5, GYP A/IFIT1B, GYP A/ITLN1, GYP A/P2RY14, GYP A/RHCE, GYP A/RNF182, GYP A/THEM5, IFIT1B/CARD17, ITLN1/CARD17, ITLN1/GLRX5, ITLN1/IFIT1B, ITLN1/RHCE, ITLN1/RNF182, ITLN1/THEM5, KLHDC8A/CARD17, KLHDC8A/GLRX5, KLHDC8A/GYP A, KLHDC8A/IFIT1B, KLHDC8A/ITLN1, KLHDC8A/P2RY14, KLHDC8A/RHCE, KLHDC8A/RNF182, KLHDC8A/SPTA1, KLHDC8A/THEM5, KLHDC8A/TSPAN5, P2RY14/GLRX5, P2RY14/IFIT1B, P2RY14/ITLN1, P2RY14/RHCE, P2RY14/RNF182, P2RY14/THEM5, RHAG/ANKRD22, RHAG/CA1, RHAG/CARD17, RHAG/CD274, RHAG/DYRK3, RHAG/FAM83A, RHAG/GBP5, RHAG/GLRX5, RHAG/GYP A, RHAG/IFIT1B, RHAG/ITLN1, RHAG/KLHDC8A, RHAG/P2RY14, RHAG/RHCE, RHAG/RNF182, RHAG/SPTA1, RHAG/THEM5, RHAG/TLCD4, RHAG/TMCC2, RHAG/TSPAN5, RHAG/TSP02, RHCE/CARD17, RHCE/IFIT1B, RHCE/THEM5, RIOK3/ANKRD22, RIOK3/BNIP3L, RIOK3/CA1, RIOK3/CARD17, RIOK3/CD274, RIOK3/DYRK3, RIOK3/FAM83A, RIOK3/GBP5, RIOK3/GLRX5, RIOK3/GYP A, RIOK3/IFIT1B, RIOK3/ITLN1, RIOK3/KLHDC8A, RIOK3/P2RY14, RIOK3/RHAG, RIOK3/RHCE, RIOK3/RNF182, RIOK3/SPTA1, RIOK3/TFEC, RIOK3/THEM5, RIOK3/TLCD4, RIOK3/TMCC2, RIOK3/TSPAN5, RIOK3/TSP02, RNF182/CARD17, RNF182/GLRX5, RNF182/IFIT1B, RNF182/RHCE, RNF182/THEM5, SPTA1/CARD17, SPTA1/GLRX5, SPTA1/GYP A, SPTA1/IFIT1B, SPTA1/ITLN1, SPTA1/P2RY14, SPTA1/RHCE, SPTA1/RNF182, SPTA1/THEM5, SPTA1/TSPAN5, TFEC/CA1, TFEC/DYRK3, TFEC/FAM83A, TFEC/GLRX5, TFEC/GYP A, TFEC/IFIT1B, TFEC/ITLN1, TFEC/KLHDC8A, TFEC/RHAG, TFEC/RHCE, TFEC/RNF182, TFEC/SPTA1, TFEC/THEM5, TFEC/TLCD4, TFEC/TMCC2, TFEC/TSPAN5, TFEC/TSP02, THEM5/CARD17, THEM5/IFIT1B, TLCD4/ANKRD22, TLCD4/CARD17, TLCD4/GBP5, TLCD4/GLRX5, TLCD4/GYP A, TLCD4/IFIT1B, TLCD4/ITLN1, TLCD4/KLHDC8A, TLCD4/P2RY14, TLCD4/RHCE, TLCD4/RNF182, TLCD4/SPTA1, TLCD4/THEM5, TLCD4/TSPAN5, TMCC2/ANKRD22, TMCC2/CA1, TMCC2/CARD17, TMCC2/DYRK3, TMCC2/FAM83A, TMCC2/GBP5, TMCC2/GLRX5, TMCC2/GYP A, TMCC2/IFIT1B, TMCC2/ITLN1, TMCC2/KLHDC8A, TMCC2/P2RY14, TMCC2/RHCE, TMCC2/RNF182, TMCC2/SPTA1, TMCC2/THEM5, TMCC2/TLCD4, TMCC2/TSPAN5, TSPAN5/CARD17, TSPAN5/GLRX5, TSPAN5/GYP A, TSPAN5/IFIT1B, TSPAN5/ITLN1, TSPAN5/P2RY14, TSPAN5/RHCE, TSPAN5/RNF182, TSPAN5/THEM5,

TSPO2/ANKRD22, TSPO2/CA1, TSPO2/CARD17, TSPO2/CD274, TSPO2/DYRK3, TSPO2/FAM83A, TSPO2/GBP5, TSPO2/GLRX5, TSPO2/GYP A, TSPO2/IFIT1B, TSPO2/ITLN1, TSPO2/KLHDC8A, TSPO2/P2RY14, TSPO2/RHCE, TSPO2/RNF182, TSPO2/SPTA1, TSPO2/THEM5, TSPO2/TLCD4, TSPO2/TMCC2, and TSPO2/TSPAN5; wherein the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1, ADAM23/GPR34, ADAM23/MAP7, ADAM23/PLCB1, ADAM23/SPRED1, ALOX15/GPR34, ALOX15/PLCB1, ALOX15/SPRED1, BAALC/GPR34, BAALC/PLCB1, BAALC/SPRED1, CACNA2D3/DYNC2H1, CACNA2D3/GPR34, CACNA2D3/PLCB1, CACNA2D3/SPRED1, CACNA2D3/ZNF600, GPR34/DYNC2H1, GPR34/GRAMD1C, GPR34/PLCB1, GPR34/TPRG1, GPR34/ZNF600, GPR82/DYNC2H1, GPR82/GPR34, GPR82/GRAMD1C, GPR82/PLCB1, GPR82/TPRG1, GPR82/ZNF600, GRAMD1C/DYNC2H1, GRAMD1C/PLCB1, GRAMD1C/ZNF600, HRK/DYNC2H1, HRK/GPR34, HRK/MAP7, HRK/PLCB1, HRK/SPRED1, HRK/ZNF600, IL5RA/DYNC2H1, IL5RA/GPR34, IL5RA/PLCB1, IL5RA/SPRED1, IL5RA/TRIM2, MAP7/BAALC, MAP7/CACNA2D3, MAP7/DYNC2H1, MAP7/GPR34, MAP7/GPR82, MAP7/GRAMD1C, MAP7/PLCB1, MAP7/SPRED1, MAP7/TPRG1, MAP7/ZNF600, PLCB1/DYNC2H1, PLCB1/TPRG1, PLCB1/ZNF600, PRSS33/GPR34, PRSS33/PLCB1, PRSS33/SPRED1, SDC2/DYNC2H1, SDC2/GPR34, SDC2/PLCB1, SDC2/ZNF600, SIGLEC8/DYNC2H1, SIGLEC8/GPR34, SIGLEC8/MAP7, SIGLEC8/PLCB1, SIGLEC8/SPRED1, SIGLEC8/TRIM2, SMPD3/DYNC2H1, SMPD3/GPR34, SMPD3/MAP7, SMPD3/PLCB1, SMPD3/SPRED1, SMPD3/TRIM2, SPRED1/DYNC2H1, SPRED1/GPR34, SPRED1/GPR82, SPRED1/GRAMD1C, SPRED1/PLCB1, SPRED1/SDC2, SPRED1/TPRG1, SPRED1/ZNF600, TRIM2/CACNA2D3, TRIM2/DYNC2H1, TRIM2/GPR34, TRIM2/GPR82, TRIM2/GRAMD1C, TRIM2/HRK, TRIM2/MAP7, TRIM2/PLCB1, TRIM2/SDC2, TRIM2/SPRED1, TRIM2/TPRG1, and TRIM2/ZNF600; wherein the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1, APOL1/BATF2, APOL1/CLEC4F, APOL1/EPSTI1, APOL1/EXOC3L1, APOL1/HES4, APOL1/IFITM3,

APOL1/LY6E, APOL1/RSAD2, APOL1/SEPTIN4, APOL1/SERPING1, APOL1/TPPP3, BATF2/EXOC3L1, BATF2/HES4, CLEC4F/BATF2, CLEC4F/EXOC3L1, EPSTI1/BATF2, EPSTI1/CLEC4F, EPSTI1/EXOC3L1, EPSTI1/HES4, EPSTI1/IFITM3, EPSTI1/LY6E, EPSTI1/RSAD2, EPSTI1/SERPING1, EPSTI1/TPPP3, ETV7/APOL1, ETV7/BATF2, ETV7/CLEC4F, ETV7/EPSTI1, ETV7/EXOC3L1, ETV7/HES4, ETV7/IFITM3, ETV7/LAMP3, ETV7/LY6E, ETV7/PLEKHO1, ETV7/RSAD2, ETV7/SEPTIN4, ETV7/SERPING1, ETV7/TPPP3, EXOC3L1/HES4, IFITM3/SERPING1, IFITM3/CLEC4F, IFITM3/TPPP3, IFITM3/LY6E, IFITM3/EXOC3L1, IFITM3/HES4, LAMP3/APOL1, LAMP3/BATF2, LAMP3/CLEC4F, LAMP3/EPSTI1, LAMP3/EXOC3L1, LAMP3/HES4, LAMP3/IFITM3, LAMP3/LY6E, LAMP3/RSAD2, LAMP3/SEPTIN4, LAMP3/SERPING1, LAMP3/TPPP3, LY6E/BATF2, LY6E/EXOC3L1, PLEKHO1/APOL1, PLEKHO1/BATF2, PLEKHO1/EPSTI1, PLEKHO1/EXOC3L1, PLEKHO1/IFITM3, PLEKHO1/LAMP3, PLEKHO1/RSAD2, PLEKHO1/SEPTIN4, PLEKHO1/SERPING1, RSAD2/BATF2, RSAD2/CLEC4F, RSAD2/EXOC3L1, RSAD2/HES4, RSAD2/IFITM3, RSAD2/LY6E, RSAD2/SERPING1, RSAD2/TPPP3, SEPTIN4/BATF2, SEPTIN4/CLEC4F, SEPTIN4/EPSTI1, SEPTIN4/EXOC3L1, SEPTIN4/HES4, SEPTIN4/IFITM3, SEPTIN4/LY6E, SEPTIN4/RSAD2, SEPTIN4/SERPING1, SEPTIN4/TPPP3, SERPING1/BATF2, SERPING1/CLEC4F, SERPING1/EXOC3L1, SERPING1/HES4, SERPING1/LY6E, SERPING1/TPPP3, TPPP3/BATF2, and TPPP3/EXOC3L1; and wherein the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL, CAV1/LGALS3BP, CAV1/OTOF, CDC45/LGALS3BP, CDC45/OTOF, CENPF/KCTD14, GPRC5D/OTOF, GTSE1/LGALS3BP, GTSE1/OTOF, IGF1/LGALS3BP, IGF1/OTOF, KCTD14/KLHL14, KCTD14/PDIA4, KCTD14/TSHR, KIF14/KCTD14, LGALS3BP/CENPF, LGALS3BP/GPRC5D, LGALS3BP/IFI27, LGALS3BP/IGLL5, LGALS3BP/KCTD14, LGALS3BP/KIF14, LGALS3BP/KIF15, LGALS3BP/KLHL14, LGALS3BP/MIR155HG, LGALS3BP/MIXL1, LGALS3BP/OTOF, LGALS3BP/PDIA4, LGALS3BP/PLAAT2, LGALS3BP/SDC1, LGALS3BP/SLC16A14, LGALS3BP/TSHR, OTOF/CENPF, OTOF/IFI27, OTOF/IGLL5, OTOF/KCTD14, OTOF/KIF14, OTOF/KIF15, OTOF/KLHL14, OTOF/MIR155HG, OTOF/MIXL1, OTOF/PDIA4, OTOF/PLAAT2,

OTOF/SDC1, OTOF/SLC16A14, OTOF/TSHR, PLAAT2/KCTD14, TNFRSF17/LGALS3BP, and TNFRSF17/OTOF.

[00126] The present disclosure also includes a kit for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the kit comprising gene specific reagents, each of the gene specific reagents capable of detecting an expression product of a respective one of a plurality of genes or complement thereof in an NPS endotype sub-signature, an INF endotype sub-signature, an IHD endotype sub-signature, an IFN endotype sub-signature, an ADA endotype sub-signature or combinations thereof; and optionally instructions for use, wherein the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, and XCR1; wherein the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC4A1, SLC6A8, SLC6A9, SLC7A5, SMIM5,

SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, and YPEL4; wherein the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, and TRIM2; wherein the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, and LAMP3; and wherein the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, USP18, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, and TTC21A.

[00127] The present disclosure also includes a kit for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the kit comprising gene specific reagents, each of the gene specific reagents capable of detecting an expression product of a respective one of a plurality of genes or complement thereof in an NPS endotype signature pair, an INF endotype signature pair, an IHD endotype signature pair, an IFN endotype signature pair, an ADA endotype signature pair or combinations thereof; and optionally instructions for use, wherein the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, MLLT1/KLF14, ADAMTS3/PCOLCE2, ADAMTS3/ZDHHC19, ADAMTS3/SLC51A, ADAMTS3/HPGD, ADAMTS3/SEMA6B, ADAMTS3/EFNA1, ADAMTS3/AGFG1, ADAMTS3/NSUN7, ADAMTS3/TNFAIP8L3, ADAMTS3/KREMEN1, ADAMTS3/ORM2, ADAMTS3/MIR646HG, ADAMTS3/KLF14, AGFG1/NSUN7, AGFG1/TNFAIP8L3, AGFG1/KREMEN1, AGFG1/ORM2, AGFG1/MIR646HG, AGFG1/KLF14, ANXA3/GPR84, ANXA3/OLAH, ANXA3/ADAMTS3, ANXA3/PCOLCE2, ANXA3/ZDHHC19, ANXA3/SLC51A, ANXA3/HPGD, ANXA3/SEMA6B,

ANXA3/EFNA1, ANXA3/AGFG1, ANXA3/NSUN7, ANXA3/TNFAIP8L3,
 ANXA3/KREMEN1, ANXA3/ORM2, ANXA3/MIR646HG, ANXA3/KLF14,
 ARG1/PFKFB2, ARG1/MLLT1, ARG1/ANXA3, ARG1/GPR84, ARG1/OLAH,
 ARG1/ADAMTS3, ARG1/PCOLCE2, ARG1/ZDHHC19, ARG1/SLC51A, ARG1/HPGD,
 ARG1/SEMA6B, ARG1/EFNA1, ARG1/AGFG1, ARG1/NSUN7, ARG1/TNFAIP8L3,
 ARG1/KREMEN1, ARG1/ORM2, ARG1/MIR646HG, ARG1/KLF14, ATP9A/EPB41L4B,
 ATP9A/IL1R1, ATP9A/GADD45A, ATP9A/ARG1, ATP9A/PFKFB2, ATP9A/MLLT1,
 ATP9A/ANXA3, ATP9A/GPR84, ATP9A/OLAH, ATP9A/ADAMTS3, ATP9A/PCOLCE2,
 ATP9A/ZDHHC19, ATP9A/SLC51A, ATP9A/HPGD, ATP9A/SEMA6B, ATP9A/EFNA1,
 ATP9A/AGFG1, ATP9A/NSUN7, ATP9A/TNFAIP8L3, ATP9A/KREMEN1,
 ATP9A/ORM2, ATP9A/MIR646HG, ATP9A/KLF14, EFNA1/AGFG1, EFNA1/NSUN7,
 EFNA1/TNFAIP8L3, EFNA1/KREMEN1, EFNA1/ORM2, EFNA1/MIR646HG,
 EFNA1/KLF14, EPB41L4B/IL1R1, EPB41L4B/GADD45A, EPB41L4B/ARG1,
 EPB41L4B/PFKFB2, EPB41L4B/MLLT1, EPB41L4B/ANXA3, EPB41L4B/GPR84,
 EPB41L4B/OLAH, EPB41L4B/ADAMTS3, EPB41L4B/PCOLCE2, EPB41L4B/ZDHHC19,
 EPB41L4B/SLC51A, EPB41L4B/HPGD, EPB41L4B/SEMA6B, EPB41L4B/EFNA1,
 EPB41L4B/AGFG1, EPB41L4B/NSUN7, EPB41L4B/TNFAIP8L3, EPB41L4B/KREMEN1,
 EPB41L4B/MIR646HG, EPB41L4B/KLF14, GADD45A/ARG1, GADD45A/PFKFB2,
 GADD45A/MLLT1, GADD45A/ANXA3, GADD45A/GPR84, GADD45A/OLAH,
 GADD45A/ADAMTS3, GADD45A/PCOLCE2, GADD45A/ZDHHC19,
 GADD45A/SLC51A, GADD45A/HPGD, GADD45A/SEMA6B, GADD45A/EFNA1,
 GADD45A/AGFG1, GADD45A/NSUN7, GADD45A/TNFAIP8L3, GADD45A/KREMEN1,
 GADD45A/ORM2, GADD45A/MIR646HG, GADD45A/KLF14, GPR84/OLAH,
 GPR84/ADAMTS3, GPR84/PCOLCE2, GPR84/ZDHHC19, GPR84/SLC51A,
 GPR84/HPGD, GPR84/SEMA6B, GPR84/EFNA1, GPR84/AGFG1, GPR84/NSUN7,
 GPR84/TNFAIP8L3, GPR84/KREMEN1, GPR84/ORM2, GPR84/MIR646HG,
 GPR84/KLF14, HPGD/SEMA6B, HPGD/EFNA1, HPGD/AGFG1, HPGD/NSUN7,
 HPGD/TNFAIP8L3, HPGD/KREMEN1, HPGD/ORM2, HPGD/MIR646HG, HPGD/KLF14,
 IL1R1/GADD45A, IL1R1/ARG1, IL1R1/PFKFB2, IL1R1/MLLT1, IL1R1/ANXA3,
 IL1R1/GPR84, IL1R1/OLAH, IL1R1/ADAMTS3, IL1R1/PCOLCE2, IL1R1/ZDHHC19,
 IL1R1/SLC51A, IL1R1/HPGD, IL1R1/SEMA6B, IL1R1/EFNA1, IL1R1/AGFG1,
 IL1R1/NSUN7, IL1R1/TNFAIP8L3, IL1R1/KREMEN1, IL1R1/ORM2, IL1R1/MIR646HG,
 IL1R1/KLF14, KREMEN1/ORM2, KREMEN1/MIR646HG, KREMEN1/KLF14,

MIR646HG/KLF14, MLLT1/ANXA3, MLLT1/GPR84, MLLT1/OLAH,
 MLLT1/ADAMTS3, MLLT1/PCOLCE2, MLLT1/ZDHHC19, MLLT1/SLC51A,
 MLLT1/HPGD, MLLT1/SEMA6B, MLLT1/EFNA1, MLLT1/AGFG1, MLLT1/NSUN7,
 MLLT1/TNFAIP8L3, MLLT1/KREMEN1, MLLT1/ORM2, MLLT1/MIR646HG,
 MLLT1/KLF14, NSUN7/TNFAIP8L3, NSUN7/KREMEN1, NSUN7/ORM2,
 NSUN7/MIR646HG, NSUN7/KLF14, OLAH/ADAMTS3, OLAH/PCOLCE2,
 OLAH/ZDHHC19, OLAH/SLC51A, OLAH/HPGD, OLAH/SEMA6B, OLAH/EFNA1,
 OLAH/AGFG1, OLAH/NSUN7, OLAH/TNFAIP8L3, OLAH/KREMEN1, OLAH/ORM2,
 OLAH/MIR646HG, OLAH/KLF14, ORM2/MIR646HG, ORM2/KLF14,
 PCOLCE2/ZDHHC19, PCOLCE2/SLC51A, PCOLCE2/HPGD, PCOLCE2/SEMA6B,
 PCOLCE2/EFNA1, PCOLCE2/AGFG1, PCOLCE2/NSUN7, PCOLCE2/TNFAIP8L3,
 PCOLCE2/KREMEN1, PCOLCE2/ORM2, PCOLCE2/MIR646HG, PCOLCE2/KLF14,
 PFKFB2/MLLT1, PFKFB2/ANXA3, PFKFB2/GPR84, PFKFB2/OLAH,
 PFKFB2/ADAMTS3, PFKFB2/PCOLCE2, PFKFB2/ZDHHC19, PFKFB2/SLC51A,
 PFKFB2/HPGD, PFKFB2/SEMA6B, PFKFB2/EFNA1, PFKFB2/AGFG1, PFKFB2/NSUN7,
 PFKFB2/TNFAIP8L3, PFKFB2/KREMEN1, PFKFB2/ORM2, PFKFB2/MIR646HG,
 PFKFB2/KLF14, SEMA6B/EFNA1, SEMA6B/AGFG1, SEMA6B/NSUN7,
 SEMA6B/TNFAIP8L3, SEMA6B/KREMEN1, SEMA6B/ORM2, SEMA6B/MIR646HG,
 SEMA6B/KLF14, SLC51A/HPGD, SLC51A/SEMA6B, SLC51A/EFNA1, SLC51A/AGFG1,
 SLC51A/NSUN7, SLC51A/TNFAIP8L3, SLC51A/KREMEN1, SLC51A/ORM2,
 SLC51A/MIR646HG, SLC51A/KLF14, TNFAIP8L3/KREMEN1, TNFAIP8L3/ORM2,
 TNFAIP8L3/MIR646HG, TNFAIP8L3/KLF14, ZDHHC19/SLC51A, ZDHHC19/HPGD,
 ZDHHC19/SEMA6B, ZDHHC19/EFNA1, ZDHHC19/AGFG1, ZDHHC19/NSUN7,
 ZDHHC19/TNFAIP8L3, ZDHHC19/KREMEN1, ZDHHC19/ORM2,
 ZDHHC19/MIR646HG, and ZDHHC19/KLF14; wherein the INF endotype signature pair is
 selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4,
 FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A,
 RHCE/FECH, TFEC/CA1, SPTA1/FECH, ANKRD22/GLRX5, ANKRD22/GYP A,
 ANKRD22/IFIT1B, ANKRD22/ITLN1, ANKRD22/KLHDC8A, ANKRD22/RHCE,
 ANKRD22/RNF182, ANKRD22/SPTA1, ANKRD22/THEM5, ANKRD22/TSPAN5,
 APOL4/BNIP3L, APOL4/CA1, APOL4/DYRK3, APOL4/FAM83A, APOL4/GLRX5,
 APOL4/GYP A, APOL4/IFIT1B, APOL4/ITLN1, APOL4/KLHDC8A, APOL4/RHAG,
 APOL4/RHCE, APOL4/RIOK3, APOL4/RNF182, APOL4/SPTA1, APOL4/THEM5,

APOL4/TLCD4, APOL4/TMCC2, APOL4/TSPAN5, APOL4/TSP02, BNIP3L/ANKRD22, BNIP3L/CA1, BNIP3L/CARD17, BNIP3L/CD274, BNIP3L/DYRK3, BNIP3L/FAM83A, BNIP3L/GBP5, BNIP3L/GLRX5, BNIP3L/GYP A, BNIP3L/IFIT1B, BNIP3L/ITLN1, BNIP3L/KLHDC8A, BNIP3L/P2RY14, BNIP3L/RHAG, BNIP3L/RHCE, BNIP3L/RNF182, BNIP3L/SPTA1, BNIP3L/TFEC, BNIP3L/THEM5, BNIP3L/TLCD4, BNIP3L/TMCC2, BNIP3L/TSPAN5, BNIP3L/TSP02, CA1/ANKRD22, CA1/CARD17, CA1/DYRK3, CA1/FAM83A, CA1/GBP5, CA1/GLRX5, CA1/GYP A, CA1/IFIT1B, CA1/ITLN1, CA1/KLHDC8A, CA1/P2RY14, CA1/RHCE, CA1/RNF182, CA1/SPTA1, CA1/THEM5, CA1/TLCD4, CA1/TSPAN5, CD274/CA1, CD274/DYRK3, CD274/FAM83A, CD274/GLRX5, CD274/GYP A, CD274/IFIT1B, CD274/ITLN1, CD274/KLHDC8A, CD274/RHCE, CD274/RNF182, CD274/SPTA1, CD274/THEM5, CD274/TLCD4, CD274/TMCC2, CD274/TSPAN5, DYRK3/ANKRD22, DYRK3/CARD17, DYRK3/FAM83A, DYRK3/GBP5, DYRK3/GLRX5, DYRK3/GYP A, DYRK3/IFIT1B, DYRK3/ITLN1, DYRK3/KLHDC8A, DYRK3/P2RY14, DYRK3/RHCE, DYRK3/RNF182, DYRK3/SPTA1, DYRK3/THEM5, DYRK3/TLCD4, DYRK3/TSPAN5, FAM83A/ANKRD22, FAM83A/CARD17, FAM83A/GBP5, FAM83A/GLRX5, FAM83A/GYP A, FAM83A/IFIT1B, FAM83A/ITLN1, FAM83A/KLHDC8A, FAM83A/P2RY14, FAM83A/RHCE, FAM83A/RNF182, FAM83A/SPTA1, FAM83A/THEM5, FAM83A/TLCD4, FAM83A/TSPAN5, FECH/ANKRD22, FECH/APOL4, FECH/BNIP3L, FECH/CA1, FECH/CARD17, FECH/CD274, FECH/DYRK3, FECH/FAM83A, FECH/GBP5, FECH/GLRX5, FECH/GYP A, FECH/IFIT1B, FECH/ITLN1, FECH/KLHDC8A, FECH/P2RY14, FECH/RHAG, FECH/RHCE, FECH/RIOK3, FECH/RNF182, FECH/SPTA1, FECH/TFEC, FECH/THEM5, FECH/TLCD4, FECH/TMCC2, FECH/TSPAN5, FECH/TSP02, GBP5/GLRX5, GBP5/GYP A, GBP5/IFIT1B, GBP5/ITLN1, GBP5/KLHDC8A, GBP5/RHCE, GBP5/RNF182, GBP5/SPTA1, GBP5/THEM5, GBP5/TSPAN5, GLRX5/CARD17, GLRX5/IFIT1B, GLRX5/RHCE, GLRX5/THEM5, GYP A/CARD17, GYP A/GLRX5, GYP A/IFIT1B, GYP A/ITLN1, GYP A/P2RY14, GYP A/RHCE, GYP A/RNF182, GYP A/THEM5, IFIT1B/CARD17, ITLN1/CARD17, ITLN1/GLRX5, ITLN1/IFIT1B, ITLN1/RHCE, ITLN1/RNF182, ITLN1/THEM5, KLHDC8A/CARD17, KLHDC8A/GLRX5, KLHDC8A/GYP A, KLHDC8A/IFIT1B, KLHDC8A/ITLN1, KLHDC8A/P2RY14, KLHDC8A/RHCE, KLHDC8A/RNF182, KLHDC8A/SPTA1, KLHDC8A/THEM5, KLHDC8A/TSPAN5, P2RY14/GLRX5, P2RY14/IFIT1B, P2RY14/ITLN1, P2RY14/RHCE,

P2RY14/RNF182, P2RY14/THEM5, RHAG/ANKRD22, RHAG/CA1, RHAG/CARD17, RHAG/CD274, RHAG/DYRK3, RHAG/FAM83A, RHAG/GBP5, RHAG/GLRX5, RHAG/GYP A, RHAG/IFIT1B, RHAG/ITLN1, RHAG/KLHDC8A, RHAG/P2RY14, RHAG/RHCE, RHAG/RNF182, RHAG/SPTA1, RHAG/THEM5, RHAG/TLCD4, RHAG/TMCC2, RHAG/TSPAN5, RHAG/TSPO2, RHCE/CARD17, RHCE/IFIT1B, RHCE/THEM5, RIOK3/ANKRD22, RIOK3/BNIP3L, RIOK3/CA1, RIOK3/CARD17, RIOK3/CD274, RIOK3/DYRK3, RIOK3/FAM83A, RIOK3/GBP5, RIOK3/GLRX5, RIOK3/GYP A, RIOK3/IFIT1B, RIOK3/ITLN1, RIOK3/KLHDC8A, RIOK3/P2RY14, RIOK3/RHAG, RIOK3/RHCE, RIOK3/RNF182, RIOK3/SPTA1, RIOK3/TFEC, RIOK3/THEM5, RIOK3/TLCD4, RIOK3/TMCC2, RIOK3/TSPAN5, RIOK3/TSPO2, RNF182/CARD17, RNF182/GLRX5, RNF182/IFIT1B, RNF182/RHCE, RNF182/THEM5, SPTA1/CARD17, SPTA1/GLRX5, SPTA1/GYP A, SPTA1/IFIT1B, SPTA1/ITLN1, SPTA1/P2RY14, SPTA1/RHCE, SPTA1/RNF182, SPTA1/THEM5, SPTA1/TSPAN5, TFEC/CA1, TFEC/DYRK3, TFEC/FAM83A, TFEC/GLRX5, TFEC/GYP A, TFEC/IFIT1B, TFEC/ITLN1, TFEC/KLHDC8A, TFEC/RHAG, TFEC/RHCE, TFEC/RNF182, TFEC/SPTA1, TFEC/THEM5, TFEC/TLCD4, TFEC/TMCC2, TFEC/TSPAN5, TFEC/TSPO2, THEM5/CARD17, THEM5/IFIT1B, TLCD4/ANKRD22, TLCD4/CARD17, TLCD4/GBP5, TLCD4/GLRX5, TLCD4/GYP A, TLCD4/IFIT1B, TLCD4/ITLN1, TLCD4/KLHDC8A, TLCD4/P2RY14, TLCD4/RHCE, TLCD4/RNF182, TLCD4/SPTA1, TLCD4/THEM5, TLCD4/TSPAN5, TMCC2/ANKRD22, TMCC2/CA1, TMCC2/CARD17, TMCC2/DYRK3, TMCC2/FAM83A, TMCC2/GBP5, TMCC2/GLRX5, TMCC2/GYP A, TMCC2/IFIT1B, TMCC2/ITLN1, TMCC2/KLHDC8A, TMCC2/P2RY14, TMCC2/RHCE, TMCC2/RNF182, TMCC2/SPTA1, TMCC2/THEM5, TMCC2/TLCD4, TMCC2/TSPAN5, TSPAN5/CARD17, TSPAN5/GLRX5, TSPAN5/GYP A, TSPAN5/IFIT1B, TSPAN5/ITLN1, TSPAN5/P2RY14, TSPAN5/RHCE, TSPAN5/RNF182, TSPAN5/THEM5, TSPO2/ANKRD22, TSPO2/CA1, TSPO2/CARD17, TSPO2/CD274, TSPO2/DYRK3, TSPO2/FAM83A, TSPO2/GBP5, TSPO2/GLRX5, TSPO2/GYP A, TSPO2/IFIT1B, TSPO2/ITLN1, TSPO2/KLHDC8A, TSPO2/P2RY14, TSPO2/RHCE, TSPO2/RNF182, TSPO2/SPTA1, TSPO2/THEM5, TSPO2/TLCD4, TSPO2/TMCC2, and TSPO2/TSPAN5; wherein the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1, ADAM23/GPR34,

ADAM23/MAP7, ADAM23/PLCB1, ADAM23/SPRED1, ALOX15/GPR34, ALOX15/PLCB1, ALOX15/SPRED1, BAALC/GPR34, BAALC/PLCB1, BAALC/SPRED1, CACNA2D3/DYNC2H1, CACNA2D3/GPR34, CACNA2D3/PLCB1, CACNA2D3/SPRED1, CACNA2D3/ZNF600, GPR34/DYNC2H1, GPR34/GRAMD1C, GPR34/PLCB1, GPR34/TPRG1, GPR34/ZNF600, GPR82/DYNC2H1, GPR82/GPR34, GPR82/GRAMD1C, GPR82/PLCB1, GPR82/TPRG1, GPR82/ZNF600, GRAMD1C/DYNC2H1, GRAMD1C/PLCB1, GRAMD1C/ZNF600, HRK/DYNC2H1, HRK/GPR34, HRK/MAP7, HRK/PLCB1, HRK/SPRED1, HRK/ZNF600, IL5RA/DYNC2H1, IL5RA/GPR34, IL5RA/PLCB1, IL5RA/SPRED1, IL5RA/TRIM2, MAP7/BAALC, MAP7/CACNA2D3, MAP7/DYNC2H1, MAP7/GPR34, MAP7/GPR82, MAP7/GRAMD1C, MAP7/PLCB1, MAP7/SPRED1, MAP7/TPRG1, MAP7/ZNF600, PLCB1/DYNC2H1, PLCB1/TPRG1, PLCB1/ZNF600, PRSS33/GPR34, PRSS33/PLCB1, PRSS33/SPRED1, SDC2/DYNC2H1, SDC2/GPR34, SDC2/PLCB1, SDC2/ZNF600, SIGLEC8/DYNC2H1, SIGLEC8/GPR34, SIGLEC8/MAP7, SIGLEC8/PLCB1, SIGLEC8/SPRED1, SIGLEC8/TRIM2, SMPD3/DYNC2H1, SMPD3/GPR34, SMPD3/MAP7, SMPD3/PLCB1, SMPD3/SPRED1, SMPD3/TRIM2, SPRED1/DYNC2H1, SPRED1/GPR34, SPRED1/GPR82, SPRED1/GRAMD1C, SPRED1/PLCB1, SPRED1/SDC2, SPRED1/TPRG1, SPRED1/ZNF600, TRIM2/CACNA2D3, TRIM2/DYNC2H1, TRIM2/GPR34, TRIM2/GPR82, TRIM2/GRAMD1C, TRIM2/HRK, TRIM2/MAP7, TRIM2/PLCB1, TRIM2/SDC2, TRIM2/SPRED1, TRIM2/TPRG1, and TRIM2/ZNF600; wherein the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1, APOL1/BATF2, APOL1/CLEC4F, APOL1/EPSTI1, APOL1/EXOC3L1, APOL1/HES4, APOL1/IFITM3, APOL1/LY6E, APOL1/RSAD2, APOL1/SEPTIN4, APOL1/SERPING1, APOL1/TPPP3, BATF2/EXOC3L1, BATF2/HES4, CLEC4F/BATF2, CLEC4F/EXOC3L1, EPSTI1/BATF2, EPSTI1/CLEC4F, EPSTI1/EXOC3L1, EPSTI1/HES4, EPSTI1/IFITM3, EPSTI1/LY6E, EPSTI1/RSAD2, EPSTI1/SERPING1, EPSTI1/TPPP3, ETV7/APOL1, ETV7/BATF2, ETV7/CLEC4F, ETV7/EPSTI1, ETV7/EXOC3L1, ETV7/HES4, ETV7/IFITM3, ETV7/LAMP3, ETV7/LY6E, ETV7/PLEKHO1, ETV7/RSAD2, ETV7/SEPTIN4, ETV7/SERPING1, ETV7/TPPP3, EXOC3L1/HES4, IFITM3/SERPING1, IFITM3/CLEC4F, IFITM3/TPPP3, IFITM3/LY6E, IFITM3/EXOC3L1, IFITM3/HES4, LAMP3/APOL1,

LAMP3/BATF2, LAMP3/CLEC4F, LAMP3/EPSTI1, LAMP3/EXOC3L1, LAMP3/HES4, LAMP3/IFITM3, LAMP3/LY6E, LAMP3/RSAD2, LAMP3/SEPTIN4, LAMP3/SERPING1, LAMP3/TPPP3, LY6E/BATF2, LY6E/EXOC3L1, PLEKHO1/APOL1, PLEKHO1/BATF2, PLEKHO1/EPSTI1, PLEKHO1/EXOC3L1, PLEKHO1/IFITM3, PLEKHO1/LAMP3, PLEKHO1/RSAD2, PLEKHO1/SEPTIN4, PLEKHO1/SERPING1, RSAD2/BATF2, RSAD2/CLEC4F, RSAD2/EXOC3L1, RSAD2/HES4, RSAD2/IFITM3, RSAD2/LY6E, RSAD2/SERPING1, RSAD2/TPPP3, SEPTIN4/BATF2, SEPTIN4/CLEC4F, SEPTIN4/EPSTI1, SEPTIN4/EXOC3L1, SEPTIN4/HES4, SEPTIN4/IFITM3, SEPTIN4/LY6E, SEPTIN4/RSAD2, SEPTIN4/SERPING1, SEPTIN4/TPPP3, SERPING1/BATF2, SERPING1/CLEC4F, SERPING1/EXOC3L1, SERPING1/HES4, SERPING1/LY6E, SERPING1/TPPP3, TPPP3/BATF2, and TPPP3/EXOC3L1; and wherein the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL, CAV1/LGALS3BP, CAV1/OTOF, CDC45/LGALS3BP, CDC45/OTOF, CENPF/KCTD14, GPRC5D/OTOF, GTSE1/LGALS3BP, GTSE1/OTOF, IGF1/LGALS3BP, IGF1/OTOF, KCTD14/KLHL14, KCTD14/PDIA4, KCTD14/TSHR, KIF14/KCTD14, LGALS3BP/CENPF, LGALS3BP/GPRC5D, LGALS3BP/IFI27, LGALS3BP/IGLL5, LGALS3BP/KCTD14, LGALS3BP/KIF14, LGALS3BP/KIF15, LGALS3BP/KLHL14, LGALS3BP/MIR155HG, LGALS3BP/MIXL1, LGALS3BP/OTOF, LGALS3BP/PDIA4, LGALS3BP/PLAAT2, LGALS3BP/SDC1, LGALS3BP/SLC16A14, LGALS3BP/TSHR, OTOF/CENPF, OTOF/IFI27, OTOF/IGLL5, OTOF/KCTD14, OTOF/KIF14, OTOF/KIF15, OTOF/KLHL14, OTOF/MIR155HG, OTOF/MIXL1, OTOF/PDIA4, OTOF/PLAAT2, OTOF/SDC1, OTOF/SLC16A14, OTOF/TSHR, PLAAT2/KCTD14, TNFRSF17/LGALS3BP, and TNFRSF17/OTOF.

[00128] The present disclosure also includes a kit for predicting severity of sepsis in a subject, wherein the severity of the sepsis is selected from high severity sepsis, intermediate severity sepsis and low severity sepsis, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5, and low severity sepsis means a SOFA score of less than 2, the kit comprising gene specific reagents, each of the gene specific reagents capable of detecting an expression product of a respective one of a plurality of genes

or complement thereof selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19; and optionally instructions for use.

[00129] In an embodiment, the gene specific reagent is a gene specific probe that is capable of detecting the expression product (e.g., nucleic acid or protein) or the complement of a nucleic acid expression product for example, wherein detection of the nucleic acid or complement thereof is subsequent to a suitable methodology for amplification. In an embodiment, the methodology for amplification comprises a polymerase chain reaction (PCR) amplification method or reverse transcriptase-(RT) PCR. Polynucleotide primers for reverse transcription of mRNA encoded by the gene, and/or for amplification of a nucleic acid sequence from the gene or from cDNA prepared from the gene encoded mRNA may also be provided in the kit.

[00130] In some embodiments, the kit comprises, consists essentially or consists of a microarray that comprises a plurality of the gene specific probes that are polynucleotides immobilized onto a solid support. In an embodiment, the microarray further comprises control polynucleotide probes specific for control sequences, such as housekeeping genes.

[00131] In an embodiment, the kit optionally further includes one or more other reagents for conducting a biological procedure, such as but not limited to buffers, salts, enzymes, enzyme co-factors, substrates, detection reagents, washing reagents, and combinations

thereof. Additional components, such as buffers and solutions for the isolation and/or treatment of a test sample, may also be included in the kit. In a further embodiment, the kit additionally comprises one or more control sequences or samples. In some embodiments, one or more of the components of the kit are lyophilized and the kit further comprises reagents suitable for the reconstitution of the lyophilized component(s).

[00132] The various components of the kit are typically provided in suitable containers. In some embodiments, the container may itself be a suitable vessel for carrying out the biological procedure, for example, a microtitre plate. Where appropriate, the kit may also optionally contain reaction vessels, mixing vessels and other components that facilitate the preparation of reagents or a test sample, or the carrying out of the biological procedure. In some embodiments, the kit further includes one or more instruments for assisting with obtaining a test sample, such as but not limited to a syringe, pipette, forceps, or combinations thereof.

[00133] In some embodiments, reagents comprised in the kit and/or their containers may be color-coded to facilitate their use. When reagents are color-coded, addition of one reagent to another in a particular step may, for example, result in a change in the color of the mixture, thus providing an indication that the step was carried out.

[00134] In an embodiment, the kit contains instructions for use, which may be provided in any suitable format such as but not limited to in paper form, in computer-readable form, and/or in the form of directions or instructions for accessing a website. In another embodiment, the kit further comprises computer readable media comprising software, and/or directions or instructions for accessing a website that provides software, for example, to assist in the interpretation of results obtained from using the kit.

[00135] It will be appreciated by a person skilled in the art that embodiments for such methods for identifying a candidate agent for the treatment of sepsis and/or kits can also be varied, as appropriate, as described herein for the corresponding embodiments in the methods for classifying a subject into a sepsis mechanistic endotype and/or methods for predicting severity of sepsis in a subject, as the case may be.

Endotype Specific Gene Signatures

[00136] GENES WITH OVERALL DISCRIMINATIVE SIGNATURE (MOST ALSO WORK IN PAIRS). NPS: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2,

PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19. **INF:** BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2. **IHD:** ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600. **IFN:** ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC. **ADA:** CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1,

[00137] OTHER GENES WITH ENDOTYPE DIAGNOSTIC POTENTIAL: NPS: ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, XCR1. **INF:** ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42, ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUNDC3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, YPEL4. **IHD:** ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, TRIM2. **IFN:** EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, LAMP3. **ADA:** AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L,

IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, TTC21A.

[00138] PREFERRED EMBODIMENTS. GENE PAIRS: NPS vs. Rest: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, MLLT1/KLF14. **INF vs. Rest:** FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, SPTA1/FECH. **IHD vs. Rest:** MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1. **IFN vs. Rest:** ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, ETV7/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1. **ADA vs. Rest:** LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL1

[00139] ADDITIONAL GENE PAIRS (AUC>0.75): NPS: ADAMTS3/PCOLCE2; ADAMTS3/ZDHHC19; ADAMTS3/SLC51A; ADAMTS3/HPGD; ADAMTS3/SEMA6B; ADAMTS3/EFNA1; ADAMTS3/AGFG1; ADAMTS3/NSUN7; ADAMTS3/TNFAIP8L3; ADAMTS3/KREMEN1; ADAMTS3/ORM2; ADAMTS3/MIR646HG; ADAMTS3/KLF14; AGFG1/NSUN7; AGFG1/TNFAIP8L3; AGFG1/KREMEN1; AGFG1/ORM2; AGFG1/MIR646HG; AGFG1/KLF14; ANXA3/GPR84; ANXA3/OLAH; ANXA3/ADAMTS3; ANXA3/PCOLCE2; ANXA3/ZDHHC19; ANXA3/SLC51A; ANXA3/HPGD; ANXA3/SEMA6B; ANXA3/EFNA1; ANXA3/AGFG1; ANXA3/NSUN7; ANXA3/TNFAIP8L3; ANXA3/KREMEN1; ANXA3/ORM2; ANXA3/MIR646HG; ANXA3/KLF14; ARG1/PFKFB2; ARG1/MLLT1; ARG1/ANXA3; ARG1/GPR84; ARG1/OLAH; ARG1/ADAMTS3; ARG1/PCOLCE2; ARG1/ZDHHC19; ARG1/SLC51A; ARG1/HPGD; ARG1/SEMA6B; ARG1/EFNA1; ARG1/AGFG1; ARG1/NSUN7; ARG1/TNFAIP8L3; ARG1/KREMEN1; ARG1/ORM2; ARG1/MIR646HG; ARG1/KLF14;

ATP9A/EPB41L4B; ATP9A/IL1R1; ATP9A/GADD45A; ATP9A/ARG1; ATP9A/PFKFB2;
 ATP9A/MLLT1; ATP9A/ANXA3; ATP9A/GPR84; ATP9A/OLAH; ATP9A/ADAMTS3;
 ATP9A/PCOLCE2; ATP9A/ZDHHC19; ATP9A/SLC51A; ATP9A/HPGD; ATP9A/EMA6B;
 ATP9A/EFNA1; ATP9A/AGFG1; ATP9A/NSUN7; ATP9A/TNFAIP8L3;
 ATP9A/KREMEN1; ATP9A/ORM2; ATP9A/MIR646HG; ATP9A/KLF14; EFNA1/AGFG1;
 EFNA1/NSUN7; EFNA1/TNFAIP8L3; EFNA1/KREMEN1; EFNA1/ORM2;
 EFNA1/MIR646HG; EFNA1/KLF14; EPB41L4B/IL1R1; EPB41L4B/GADD45A;
 EPB41L4B/ARG1; EPB41L4B/PFKFB2; EPB41L4B/LLT1; EPB41L4B/ANXA3;
 EPB41L4B/GPR84; EPB41L4B/OLAH; EPB41L4B/ADAMTS3; EPB41L4B/PCOLCE2;
 EPB41L4B/ZDHHC19; EPB41L4B/SLC51A; EPB41L4B/HPGD; EPB41L4B/SEMA6B;
 EPB41L4B/EFNA1; EPB41L4B/AGFG1; EPB41L4B/NSUN7; EPB41L4B/TNFAIP8L3;
 EPB41L4B/KREMEN1; EPB41L4B/MIR646HG; EPB41L4B/KLF14; GADD45A/ARG1;
 GADD45A/PFKFB2; GADD45A/MLLT1; GADD45A/ANXA3; GADD45A/GPR84;
 GADD45A/OLAH; GADD45A/ADAMTS3; GADD45A/PCOLCE2; GADD45A/ZDHHC19;
 GADD45A/SLC51A; GADD45A/HPGD; GADD45A/SEMA6B; GADD45A/EFNA1;
 GADD45A/AGFG1; GADD45A/NSUN7; GADD45A/TNFAIP8L3; GADD45A/KREMEN1;
 GADD45A/ORM2; GADD45A/MIR646HG; GADD45A/KLF14; GPR84/OLAH;
 GPR84/ADAMTS3; GPR84/PCOLCE2; GPR84/ZDHHC19; GPR84/SLC51A;
 GPR84/HPGD; GPR84/SEMA6B; GPR84/EFNA1; GPR84/AGFG1; GPR84/NSUN7;
 GPR84/TNFAIP8L3; GPR84/KREMEN1; GPR84/ORM2; GPR84/MIR646HG;
 GPR84/KLF14; HPGD/SEMA6B; HPGD/EFNA1; HPGD/AGFG1; HPGD/NSUN7;
 HPGD/TNFAIP8L3; HPGD/KREMEN1; HPGD/ORM2; HPGD/MIR646HG; HPGD/KLF14;
 IL1R1/GADD45A; IL1R1/ARG1; IL1R1/PFKFB2; IL1R1/MLLT1; IL1R1/ANXA3;
 IL1R1/GPR84; IL1R1/OLAH; IL1R1/ADAMTS3; IL1R1/PCOLCE2; IL1R1/ZDHHC19;
 IL1R1/SLC51A; IL1R1/HPGD; IL1R1/SEMA6B; IL1R1/EFNA1; IL1R1/AGFG1;
 IL1R1/NSUN7; IL1R1/TNFAIP8L3; IL1R1/KREMEN1; IL1R1/ORM2; IL1R1/MIR646HG;
 IL1R1/KLF14; KREMEN1/ORM2; KREMEN1/MIR646HG; KREMEN1/KLF14;
 MIR646HG/KLF14; MLLT1/ANXA3; MLLT1/GPR84; MLLT1/OLAH;
 MLLT1/ADAMTS3; MLLT1/PCOLCE2; MLLT1/ZDHHC19; MLLT1/SLC51A;
 MLLT1/HPGD; MLLT1/SEMA6B; MLLT1/EFNA1; MLLT1/AGFG1; MLLT1/SUN7;
 MLLT1/TNFAIP8L3; MLLT1/KREMEN1; MLLT1/ORM2; MLLT1/MIR646HG;
 MLLT1/KLF14; NSUN7/TNFAIP8L3; NSUN7/KREMEN1; NSUN7/ORM2;
 NSUN7/MIR646HG; NSUN7/KLF14; OLAH/ADAMTS3; OLAH/PCOLCE2;

OLAH/ZDHHC19; OLAH/SLC51A; OLAH/HPGD; OLAH/SEMA6B; OLAH/EFNA1;
 OLAH/AGFG1; OLAH/NSUN7; OLAH/TNFAIP8L3; OLAH/KREMEN1; OLAH/ORM2;
 OLAH/MIR646HG; OLAH/KLF14; ORM2/MIR646HG; ORM2/KLF14;
 PCOLCE2/ZDHHC19; PCOLCE2/SLC51A; PCOLCE2/HPGD; PCOLCE2/SEMA6B;
 PCOLCE2/EFNA1; PCOLCE2/AGFG1; PCOLCE2/NSUN7; PCOLCE2/TNFAIP8L3;
 PCOLCE2/KREMEN1; PCOLCE2/ORM2; PCOLCE2/MIR646HG; PCOLCE2/KLF14;
 PFKFB2/MLLT1; PFKFB2/ANXA3; PFKFB2/GPR84; PFKFB2/OLAH;
 PFKFB2/ADAMTS3; PFKFB2/PCOLCE2; PFKFB2/ZDHHC19; PFKFB2/SLC51A;
 PFKFB2/HPGD; PFKFB2/SEMA6B; PFKFB2/EFNA1; PFKFB2/AGFG1; PFKFB2/NSUN7;
 PFKFB2/TNFAIP8L3; PFKFB2/KREMEN1; PFKFB2/ORM2; PFKFB2/MIR646HG;
 PFKFB2/KLF14; SEMA6B/EFNA1; SEMA6B/AGFG1; SEMA6B/NSUN7;
 SEMA6B/TNFAIP8L3; SEMA6B/KREMEN1; SEMA6B/ORM2; SEMA6B/MIR646HG;
 SEMA6B/KLF14; SLC51A/HPGD; SLC51A/SEMA6B; SLC51A/EFNA1;
 SLC51A/AGFG1; SLC51A/NSUN7; SLC51A/TNFAIP8L3; SLC51A/KREMEN1;
 SLC51A/ORM2; SLC51A/MIR646HG; SLC51A/KLF14; TNFAIP8L3/KREMEN1;
 TNFAIP8L3/ORM2; TNFAIP8L3/MIR646HG; TNFAIP8L3/KLF14; ZDHHC19/SLC51A;
 ZDHHC19/HPGD; ZDHHC19/SEMA6B; ZDHHC19/EFNA1; ZDHHC19/AGFG1;
 ZDHHC19/NSUN7; ZDHHC19/TNFAIP8L3; ZDHHC19/KREMEN1; ZDHHC19/ORM2;
 ZDHHC19/MIR646HG; ZDHHC19/KLF14; INF: ANKRD22/GLRX5; ANKRD22/GYP A;
 ANKRD22/IFIT1B; ANKRD22/ITLN1; ANKRD22/KLHDC8A; ANKRD22/RHCE;
 ANKRD22/RNF182; ANKRD22/SPTA1; ANKRD22/THEM5; ANKRD22/TSPAN5;
 APOL4/BNIP3L; APOL4/CA1; APOL4/DYRK3; APOL4/FAM83A; APOL4/GLRX5;
 APOL4/GYP A; APOL4/IFIT1B; APOL4/ITLN1; APOL4/KLHDC8A; APOL4/RHAG;
 APOL4/RHCE; APOL4/RIOK3; APOL4/RNF182; APOL4/SPTA1; APOL4/THEM5;
 APOL4/TLCD4; APOL4/TMCC2; APOL4/TSPAN5; APOL4/TSP02; BNIP3L/ANKRD22;
 BNIP3L/CA1; BNIP3L/CARD17; BNIP3L/CD274; BNIP3L/DYRK3; BNIP3L/FAM83A;
 BNIP3L/GBP5; BNIP3L/GLRX5; BNIP3L/GYP A; BNIP3L/IFIT1B; BNIP3L/ITLN1;
 BNIP3L/KLHDC8A; BNIP3L/P2RY14; BNIP3L/RHAG; BNIP3L/RHCE; BNIP3L/RNF182;
 BNIP3L/SPTA1; BNIP3L/TFEC; BNIP3L/THEM5; BNIP3L/TLCD4; BNIP3L/TMCC2;
 BNIP3L/TSPAN5; BNIP3L/TSP02; CA1/ANKRD22; CA1/CARD17; CA1/DYRK3;
 CA1/FAM83A; CA1/GBP5; CA1/GLRX5; CA1/GYP A; CA1/IFIT1B; CA1/ITLN1;
 CA1/KLHDC8A; CA1/P2RY14; CA1/RHCE; CA1/RNF182; CA1/SPTA1; CA1/THEM5;
 CA1/TLCD4; CA1/TSPAN5; CD274/CA1; CD274/DYRK3; CD274/FAM83A;

CD274/GLRX5; CD274/GYP A; CD274/IFIT1B; CD274/ITLN1; CD274/KLHDC8A;
 CD274/RHCE; CD274/RNF182; CD274/SPTA1; CD274/THEM5; CD274/TLCD4;
 CD274/TMCC2; CD274/TSPAN5; DYRK3/ANKRD22; DYRK3/CARD17;
 DYRK3/FAM83A; DYRK3/GBP5; DYRK3/GLRX5; DYRK3/GYP A; DYRK3/IFIT1B;
 DYRK3/ITLN1; DYRK3/KLHDC8A; DYRK3/P2RY14; DYRK3/RHCE; DYRK3/RNF182;
 DYRK3/SPTA1; DYRK3/THEM5; DYRK3/TLCD4; DYRK3/TSPAN5;
 FAM83A/ANKRD22; FAM83A/CARD17; FAM83A/GBP5; FAM83A/GLRX5;
 FAM83A/GYP A; FAM83A/IFIT1B; FAM83A/ITLN1; FAM83A/KLHDC8A;
 FAM83A/P2RY14; FAM83A/RHCE; FAM83A/RNF182; FAM83A/SPTA1;
 FAM83A/THEM5; FAM83A/TLCD4; FAM83A/TSPAN5; FECH/ANKRD22;
 FECH/APOL4; FECH/BNIP3L; FECH/CA1; FECH/CARD17; FECH/CD274;
 FECH/DYRK3; FECH/FAM83A; FECH/GBP5; FECH/GLRX5; FECH/GYP A;
 FECH/IFIT1B; FECH/ITLN1; FECH/KLHDC8A; FECH/P2RY14; FECH/RHAG;
 FECH/RHCE; FECH/RIOK3; FECH/RNF182; FECH/SPTA1; FECH/TFEC; FECH/THEM5;
 FECH/TLCD4; FECH/TMCC2; FECH/TSPAN5; FECH/TSPO2; GBP5/GLRX5;
 GBP5/GYP A; GBP5/IFIT1B; GBP5/ITLN1; GBP5/KLHDC8A; GBP5/RHCE;
 GBP5/RNF182; GBP5/SPTA1; GBP5/THEM5; GBP5/TSPAN5; GLRX5/CARD17;
 GLRX5/IFIT1B; GLRX5/RHCE; GLRX5/THEM5; GYP A/CARD17; GYP A/GLRX5;
 GYP A/IFIT1B; GYP A/ITLN1; GYP A/P2RY14; GYP A/RHCE; GYP A/RNF182;
 GYP A/THEM5; IFIT1B/CARD17; ITLN1/CARD17; ITLN1/GLRX5; ITLN1/IFIT1B;
 ITLN1/RHCE; ITLN1/RNF182; ITLN1/THEM5; KLHDC8A/CARD17;
 KLHDC8A/GLRX5; KLHDC8A/GYP A; KLHDC8A/IFIT1B; KLHDC8A/ITLN1;
 KLHDC8A/P2RY14; KLHDC8A/RHCE; KLHDC8A/RNF182; KLHDC8A/SPTA1;
 KLHDC8A/THEM5; KLHDC8A/TSPAN5; P2RY14/GLRX5; P2RY14/IFIT1B;
 P2RY14/ITLN1; P2RY14/RHCE; P2RY14/RNF182; P2RY14/THEM5; RHAG/ANKRD22;
 RHAG/CA1; RHAG/CARD17; RHAG/CD274; RHAG/DYRK3; RHAG/FAM83A;
 RHAG/GBP5; RHAG/GLRX5; RHAG/GYP A; RHAG/IFIT1B; RHAG/ITLN1;
 RHAG/KLHDC8A; RHAG/P2RY14; RHAG/RHCE; RHAG/RNF182; RHAG/SPTA1;
 RHAG/THEM5; RHAG/TLCD4; RHAG/TMCC2; RHAG/TSPAN5; RHAG/TSPO2;
 RHCE/CARD17; RHCE/IFIT1B; RHCE/THEM5; RIOK3/ANKRD22; RIOK3/BNIP3L;
 RIOK3/CA1; RIOK3/CARD17; RIOK3/CD274; RIOK3/DYRK3; RIOK3/FAM83A;
 RIOK3/GBP5; RIOK3/GLRX5; RIOK3/GYP A; RIOK3/IFIT1B; RIOK3/ITLN1;
 RIOK3/KLHDC8A; RIOK3/P2RY14; RIOK3/RHAG; RIOK3/RHCE; RIOK3/RNF182;

RIOK3/SPTA1; RIOK3/TFEC; RIOK3/THEM5; RIOK3/TLCD4; RIOK3/TMCC2;
 RIOK3/TSPAN5; RIOK3/TSPO2; RNF182/CARD17; RNF182/GLRX5; RNF182/IFIT1B;
 RNF182/RHCE; RNF182/THEM5; SPTA1/CARD17; SPTA1/GLRX5; SPTA1/GYP A;
 SPTA1/IFIT1B; SPTA1/ITLN1; SPTA1/P2RY14; SPTA1/RHCE; SPTA1/RNF182;
 SPTA1/THEM5; SPTA1/TSPAN5; TFEC/CA1; TFEC/DYRK3; TFEC/FAM83A;
 TFEC/GLRX5; TFEC/GYP A; TFEC/IFIT1B; TFEC/ITLN1; TFEC/KLHDC8A;
 TFEC/RHAG; TFEC/RHCE; TFEC/RNF182; TFEC/SPTA1; TFEC/THEM5; TFEC/TLCD4;
 TFEC/TMCC2; TFEC/TSPAN5; TFEC/TSPO2; THEM5/CARD17; THEM5/IFIT1B;
 TLCD4/ANKRD22; TLCD4/CARD17; TLCD4/GBP5; TLCD4/GLRX5; TLCD4/GYP A;
 TLCD4/IFIT1B; TLCD4/ITLN1; TLCD4/KLHDC8A; TLCD4/P2RY14; TLCD4/RHCE;
 TLCD4/RNF182; TLCD4/SPTA1; TLCD4/THEM5; TLCD4/TSPAN5; TMCC2/ABCA6;
 TMCC2/ANKRD22; TMCC2/CA1; TMCC2/CARD17; TMCC2/DYRK3;
 TMCC2/FAM83A; TMCC2/GBP5; TMCC2/GLRX5; TMCC2/GYP A; TMCC2/IFIT1B;
 TMCC2/ITLN1; TMCC2/KLHDC8A; TMCC2/P2RY14; TMCC2/RHCE; TMCC2/RNF182;
 TMCC2/SPTA1; TMCC2/THEM5; TMCC2/TLCD4; TMCC2/TSPAN5; TSPAN5/CARD17;
 TSPAN5/GLRX5; TSPAN5/GYP A; TSPAN5/IFIT1B; TSPAN5/ITLN1; TSPAN5/P2RY14;
 TSPAN5/RHCE; TSPAN5/RNF182; TSPAN5/THEM5; TSPO2/ANKRD22; TSPO2/CA1;
 TSPO2/CARD17; TSPO2/CD274; TSPO2/DYRK3; TSPO2/FAM83A; TSPO2/GBP5;
 TSPO2/GLRX5; TSPO2/GYP A; TSPO2/IFIT1B; TSPO2/ITLN1; TSPO2/KLHDC8A;
 TSPO2/P2RY14; TSPO2/RHCE; TSPO2/RNF182; TSPO2/SPTA1; TSPO2/THEM5;
 TSPO2/TLCD4; TSPO2/TMCC2; TSPO2/TSPAN5; **IHD:** ADAM23/GPR34;
 ADAM23/MAP7; ADAM23/PLCB1; ADAM23/SPRED1; ALOX15/GPR34;
 ALOX15/PLCB1; ALOX15/SPRED1; BAALC/GPR34; BAALC/PLCB1; BAALC/SPRED1;
 CACNA2D3/DYNC2H1; CACNA2D3/GPR34; CACNA2D3/PLCB1;
 CACNA2D3/SPRED1; CACNA2D3/ZNF600; GPR34/DYNC2H1; GPR34/GRAMD1C;
 GPR34/PLCB1; GPR34/PRG1; GPR34/ZNF600; GPR82/DYNC2H1; GPR82/GPR34;
 GPR82/GRAMD1C; GPR82/PLCB1; GPR82/TPRG1; GPR82/ZNF600;
 GRAMD1C/DYNC2H1; GRAMD1C/PLCB1; GRAMD1C/ZNF600; HRK/DYNC2H1;
 HRK/GPR34; HRK/MAP7; HRK/PLCB1; HRK/SPRED1; HRK/ZNF600;
 IL5RA/DYNC2H1; IL5RA/GPR34; IL5RA/PLCB1; IL5RA/SPRED1; IL5RA/TRIM2;
 MAP7/BAALC; MAP7/CACNA2D3; MAP7/DYNC2H1; MAP7/GPR34; MAP7/GPR82;
 MAP7/GRAMD1C; MAP7/PLCB1; MAP7/SPRED1; MAP7/TPRG1; MAP7/ZNF600;
 PLCB1/DYNC2H1; PLCB1/TPRG1; PLCB1/ZNF600; PRSS33/GPR34; PRSS33/PLCB1;

PRSS33/SPRED1; SDC2/DYNC2H1; SDC2/GPR34; SDC2/PLCB1; SDC2/ZNF600;
 SIGLEC8/DYNC2H1; SIGLEC8/GPR34; SIGLEC8/MAP7; SIGLEC8/PLCB1;
 SIGLEC8/SPRED1; SIGLEC8/TRIM2; SMPD3/DYNC2H1; SMPD3/GPR34;
 SMPD3/MAP7; SMPD3/PLCB1; SMPD3/SPRED1; SMPD3/TRIM2; SPRED1/DYNC2H1;
 SPRED1/GPR34; SPRED1/GPR82; SPRED1/GRAMD1C; SPRED1/PLCB1;
 SPRED1/SDC2; SPRED1/TPRG1; SPRED1/ZNF600; TRIM2/CACNA2D3;
 TRIM2/DYNC2H1; TRIM2/GPR34; TRIM2/GPR82; TRIM2/GRAMD1C; TRIM2/HRK;
 TRIM2/MAP7; TRIM2/PLCB1; TRIM2/SDC2; TRIM2/SPRED1; TRIM2/TPRG1;
 TRIM2/ZNF600; **IFN:** APOL1/BATF2; APOL1/CLEC4F; APOL1/EPSTI1;
 APOL1/EXOC3L1; APOL1/HES4; APOL1/IFITM3; APOL1/LY6E; APOL1/RSAD2;
 APOL1/SEPTIN4; APOL1/SERPING1; APOL1/TPPP3; BATF2/EXOC3L1; BATF2/HES4;
 CLEC4F/BATF2; CLEC4F/EXOC3L1; EPSTI1/BATF2; EPSTI1/CLEC4F;
 EPSTI1/EXOC3L1; EPSTI1/HES4; EPSTI1/IFITM3; EPSTI1/LY6E; EPSTI1/RSAD2;
 EPSTI1/SERPING1; EPSTI1/TPPP3; ETV7/APOL1; ETV7/BATF2; ETV7/CLEC4F;
 ETV7/EPSTI1; ETV7/EXOC3L1; ETV7/HES4; ETV7/IFITM3; ETV7/LAMP3;
 ETV7/LY6E; ETV7/PLEKHO1; ETV7/RSAD2; ETV7/SEPTIN4; ETV7/SERPING1;
 ETV7/TPPP3; EXOC3L1/HES4; LAMP3/APOL1; LAMP3/BATF2; LAMP3/CLEC4F;
 LAMP3/EPSTI1; LAMP3/EXOC3L1; LAMP3/HES4; LAMP3/IFITM3; LAMP3/LY6E;
 LAMP3/RSAD2; LAMP3/SEPTIN4; LAMP3/SERPING1; LAMP3/TPPP3; LY6E/BATF2;
 LY6E/EXOC3L1; PLEKHO1/APOL1; PLEKHO1/BATF2; PLEKHO1/EPSTI1;
 PLEKHO1/EXOC3L1; PLEKHO1/IFITM3; PLEKHO1/LAMP3; PLEKHO1/RSAD2;
 PLEKHO1/SEPTIN4; PLEKHO1/SERPING1; RSAD2/BATF2; RSAD2/CLEC4F;
 RSAD2/EXOC3L1; RSAD2/HES4; RSAD2/IFITM3; RSAD2/LY6E; RSAD2/SERPING1;
 RSAD2/TPPP3; SEPTIN4/BATF2; SEPTIN4/CLEC4F; SEPTIN4/EPSTI1;
 SEPTIN4/EXOC3L1; SEPTIN4/HES4; SEPTIN4/IFITM3; SEPTIN4/LGALS3BP;
 SEPTIN4/LY6E; SEPTIN4/OTOF; SEPTIN4/RSAD2; SEPTIN4/SERPING1;
 SEPTIN4/TPPP3; SERPING1/BATF2; SERPING1/CLEC4F; SERPING1/EXOC3L1;
 SERPING1/HES4; SERPING1/LY6E; SERPING1/TPPP3; TPPP3/BATF2;
 TPPP3/EXOC3L1; **ADA:** CAV1/LGALS3BP; CAV1/OTOF; CDC45/LGALS3BP;
 CDC45/OTOF; CENPF/KCTD14; GPRC5D/OTOF; GTSE1/LGALS3BP; GTSE1/OTOF;
 IGF1/LGALS3BP; IGF1/OTOF; KCTD14/KLHL14; KCTD14/PDIA4; KCTD14/TSHR;
 KIF14/KCTD14; LGALS3BP/CENPF; LGALS3BP/GPRC5D; LGALS3BP/IFI27;
 LGALS3BP/IGLL5; LGALS3BP/KCTD14; LGALS3BP/KIF14; LGALS3BP/KIF15;

LGALS3BP/KLHL14; LGALS3BP/MIR155HG; LGALS3BP/MIXL1; LGALS3BP/OTOF; LGALS3BP/PDIA4; LGALS3BP/PLAAT2; LGALS3BP/SDC1; LGALS3BP/SLC16A14; LGALS3BP/TSHR; OTOF/CENPF; OTOF/IFI27; OTOF/IGLL5; OTOF/KCTD14; OTOF/KIF14; OTOF/KIF15; OTOF/KLHL14; OTOF/MIR155HG; OTOF/MIXL1; OTOF/PDIA4; OTOF/PLAAT2; OTOF/SDC1; OTOF/SLC16A14; OTOF/TSHR; PLAAT2/KCTD14; TNFRSF17/LGALS3BP; TNFRSF17/OTOF;

[00140] GENE SEVERITY SIGNATURE: ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, ZDHHC19

[00141] REDUCED GENE SEVERITY SIGNATURES. (1) CCL4L2, GPR84, HRK, MMP8, GGT5, RASGRF1; (2) ADAMTS2, RETN, MMP8, G0S2, CYP19A1, OLAH, SLC6A19, TNFAIP8L3.

[00142] The following non-limiting examples are illustrative of the present disclosure:

EXAMPLES

I. Methods

(a) Study Design and Clinical Data Collection

[00143] FIG. 1 shows the general study design. We enrolled adult patients (>18 years of age) with suspected sepsis, under ethical approval, within two hours of emergency room (ER) admission. Ethics approvals were obtained for all sequencing and bioinformatics studies, carried out in a manner blinded to patient identity. Suspicion of sepsis was based on the attending physician's informed opinion, with patients meeting Sepsis-3 criteria [Singer et al. 2016] or showing at least two SIRS criteria [Bone RC et al. Chest. 1992;101:1644-1655. doi:10.1378/chest.101.6.1644] and suspicion of infection. Patients were excluded if death was impending (within 12 hours), if blood collection was unattainable, or consent was withheld. Enrollment included a full spectrum of individuals who might be suspected of being pre-septic, and while aware of the possibility that early therapy can strongly influence outcomes for such patients, we made no attempt to correct for treatments that might influence outcome measures since we were interested in the underlying mechanisms.

[00144] To enable retrospective association with gene expression data, various clinical metadata were collected at triage and within the 72 hours following ER admission, including demographics, ER test results reflecting signs of inflammation and infection, treatment data, and severity and outcome-specific clinical data, including measures of organ failure. In total 115 patients were recruited from ERs in Groningen, Netherlands (104) and Vancouver, Canada (11; sample collection limited by the SARS-CoV-2 pandemic). In addition, we recruited a cohort of 82 patients admitted to a Toronto, Canada tertiary care ICU with suspicion of pulmonary sepsis with and/or without Covid-19. Of these, 27 were confirmed to be infected with SARS-CoV-2 by subsequent viral PCR. Healthy control samples were also obtained from those who were either surgical controls or healthy volunteers (n = 9).

(b) Blood collection and RNA-Seq

[00145] During usual ER blood sample collections for suspected sepsis patients, an additional 3 ml of blood was collected for RNA-Seq. Blood was collected in PAXgene™ Blood RNA tubes (BD Biosciences; San Jose, CA, USA) to ensure stabilization of intracellular RNA. After freezing, these were transported to Vancouver where RNA isolation and sample preparation was performed according to an established standard operating procedure (SOP)

used in the REW Hancock lab (Lee, A.H. et al. Nature Communications 2019;10(1):1092). Total RNA was extracted using PAXgene Blood RNA Kit (Qiagen; Germantown, MD, USA). Quantification and quality measures of total RNA were obtained using an AgilentTM 2100 Bioanalyzer (Agilent; Santa Clara, USA). Poly-adenylated RNA was captured using NEBNextTM Poly(A) mRNA Magnetic Isolation Module (NEB; Ipswich, USA). cDNA libraries were prepared using the KAPATM Total RNA HyperPrep Kit (Roche; Basel, Switzerland). RNA-Seq was then performed on IlluminaTM Hi-Seq instrument using single read runs of 150 base-pair long sequence reads (excluding adapter/index sequences). Samples with RNA Integrity Numbers (RIN) below 6.5 were not sequenced. A standard data processing protocol was used [Lee AH et al. Nature Comm. 2019;10:1092. doi.org/10.1038/s41467-019-08794-x], including quality control using fastqc (v0.11.7) and multiqc (v1.6), alignment to the human genome (Ensembl GRCh38.92) using STAR (v2.6.0a), and read count assessments using htseq-count (v0.11.0). Finally, globin genes and genes with fewer than 10 counts were removed from count tables, and samples with fewer than one million total counts were not further analyzed. A variance stabilizing transformation (VST) was performed to render counts homoscedastic and normalized for varying library sizes. Following transformation, technical variation due to sequencing batch was removed using ComBat within the Surrogate Variable Analysis R package (3.30.1). Gene expression from the discovery and validation cohorts were treated independently of each other prior to VST normalization and batch correction to avoid signal leakage (also referred to as train-test leakage).

(c) Cluster validation and consensus clustering

[00146] In identifying subgroups or endotypes of a disease, one is trying to uncover genetic or clinical features that are common to a given subset of patients. The assumption is that patients with similar profiles share underlying mechanisms and outcomes and thus should be identified and treated accordingly. Cluster analysis or unsupervised data mining is the task of dividing a set of samples into a defined number of groups. Samples in the same group are more similar to samples in the same group when compared to samples in other groups.

[00147] Determining the optimal number of subgroups or clusters in a given disease, or more generally a data matrix is complex. In the absence of extensive domain knowledge and to avoid subjective decision making, we employed, to determine the number of sepsis endotypes, various empirical validity metrics, including consensus clustering cumulative distribution functions [Wilkerson MD, Hayes DN. Bioinformatics Appl. Note. 2010;26:1572-1573.

doi:10.1093/bioinformatics/btq170], Gap Statistic, Silhouette, Connectivity. We evaluated k values ranging from two to ten and applied validation metrics to determine the optimal number of clusters present. Further, to minimize the impact of noisy and irrelevant genes on the clustering results, we ranked genes by variance (mean absolute deviation) and performed cluster validation on the clustering inputs made up of the top 10 to 100 percent of genes (examining the top 10%, 25%, 50%, 75%, and 100% of genes). The optimal number of clusters was recorded for each clustering input for each cluster validation metric. Ultimately, the clustering input and k cluster value that were stable using the fewest input genes, were selected. We found that k cluster values of five and two were optimal using input genes for the top 10% of genes. To more broadly explore the diversity in transcriptional responses and underlying mechanisms, and enable further biological and clinical characterization, we selected 5 clusters.

[00148] Consensus k -medoids clustering was used to cluster patients on the basis of gene expression profiles. Consensus clustering, also referred to as ensemble clustering, is an algorithm that performs repeated clustering on subsamples of a portion of samples and genes. K -medoids with Manhattan distance was used for clustering since it is more robust to outliers, which are common in high-throughput omics data, when compared to other methods such as hierarchical clustering. Consensus clustering provided a consensus of the repeated clustering, which was robust to sampling variability. The consensus was represented as a consensus matrix, where each element is the fraction of times that two samples clustered together. Thus, a perfectly stable consensus matrix would consist of a matrix of 1's and 0's. The stability of the consensus matrix was quantified by CDF and area-under-the-CDF (AUCDF) plots.

(d) Bioinformatics and statistical analysis

[00149] To determine the separation of clusters based on global gene expression, principal component analysis (PCA), differential expression relative to healthy controls, and functional pathway enrichment were explored. Dysregulated genes were identified in each endotype relative to healthy controls using DESeq2-based differential expression [Love MI et al. *Genome Bio.* 2014;15:550. doi:10.1186/s13059-014-0550-8]. Endotypes were compared to a set of healthy control patients, with a separate set held out for the validation cohorts. A gene was considered differentially expressed (DE) if its absolute value fold change was ≥ 2 with an adjusted P value ≤ 0.01 . Functional characterization of differential expression was performed using an overrepresentation analysis (or enrichment analysis) of Reactome pathways, using the ReactomePA package [Fabregat A, et al. *Nucleic Acids Res.* 2018.

doi:10.1093/nar/gkx1132]. A pathway was considered enriched if its adjusted P value ≤ 0.01 . The pathway ratio represented the number of differentially expressed genes from that pathway relative to the total number of genes in the pathway. Cell proportions were estimated using the program CIBERSORT [<https://cibersort.stanford.edu/>; see, for example: Newman et al., 2015], since measured cell counts and differentials were not collected for several patients. Clinical measurements/variables were compared between clusters using non-parametric comparison of rank statistics (Kruskal-Wallis tests) and Chi-square tests depending on the variable type. The endotypes were compared in the context of impending severity and outcomes, as measured by sequential organ failure assessment (SOFA scores measured 24 and 72 hours post admission, length of hospital stay, treatments, ICU admission and mortality.

[00150] Subsequently gene expression signatures were identified by comparing global gene expression profiles between endotypes using differential expression analysis (top 200 differentially expressed genes when comparing each endotype to all others). This reflected the unique biological character of each endotype as revealed by plotting the gene expression differences onto protein:protein interaction (PPI) networks using NetworkAnalyst [Zhou G, et al. *Nucleic Acids Res.* 2019;47(W1):W234-W241]. Since protein:protein interactions (physical, metabolic or regulatory interactions) reveal the functionally-based interactions of individual proteins, the formation of tight and discrete networks indicated strong mechanistic differences between individual endotypes. In addition, gene set variation analysis (GSVA, an unsupervised method that calculates per sample enrichment scores as a function of gene expression inside and outside the gene set) [Hänzelmann S, et al. *BMC Bioinformatics.* 2013;14:7. doi:10.1186/1471-2105-14-7] was used to assess the enrichment of the 200-gene signatures in each patient, which demonstrated that the signature corresponding to a single associated endotype was highly enriched in each of the classified patients. A classification scheme was derived for the endotype model using a supervised machine learning model, namely multinomial regression with least absolute shrinkage and selection operator (LASSO) [Tibshirani R. *J. Royal Statistical Soc. B* 2011;73:273–282] regularization. The trained multinomial endotype model was applied to each patient's gene expression profile (using the genes and model parameters) in the ICU validation cohorts to predict endotype status.

[00151] For some patients, the overall predicted prognoses for any given endotype was not accurate based on patient SOFA scores, ICU admission, and mortality. While not wishing to be limited by theory, this could reflect rapid and successful treatments like antibiotics to

prevent further progression, or patient genetic background, or existing conditions that might influence deterioration. To this end, we characterized severity groups in a fashion similar to the endotypes, and built logistic regression models to predict severity groups. The goal was to identify gene signatures relevant to current definitions of sepsis. The Third International consensus definition of sepsis (Sepsis-3; Singer et al. 2016) includes SOFA as a proxy for organ dysfunction and sepsis, with increases in the SOFA score reflecting increases in mortality risk. The ER and ICU patients were combined to obtain a wide range of patient severity, based on SOFA scores measured 24 hours post ER/ICU admission. Patients were assigned to High (24-hour post ER/ICU admission SOFA scores ≥ 5 ; $n = 60$), Intermediate (SOFA ≥ 2 and <5 ; $n = 67$), and Low (SOFA <2 , $n = 67$) severity groups. Similar to endotype characterization, gene expression profiles of severity groups were compared to healthy controls and to each other using differential expression and pathway enrichment.

II. Results and Discussion

(a) Stratification of ER patients with suspicion of sepsis into five clusters

[00152] Endotypes are subgroups of a condition, wherein each endotype is defined by distinct biological mechanisms, and they are clinically relevant. Several clinical trials have been unsuccessful in identifying biomarkers specific to sepsis [Marshall JC. Trends Molec. Med. 2014;20:195-203. doi:10.1016/j.molmed.2014.01.007] while not wishing to be limited by theory, likely because the presence of heterogeneous subgroups is ignored. Results to date, largely driven by analysis of patient metadata and microarray transcriptomic studies, have indicated specific endotypes that have significantly higher severity scores and progress to worse outcomes; therefore, identifying endotype status early may permit aggressive interventions to prevent further progression of sepsis. Accordingly, the primary motivation for identifying endotypes in sepsis, particularly in its earliest stages, has been to dissect the heterogeneous molecular responses at play. Including a broad spectrum of patients also allowed us to identify possible molecular features differentiating sepsis and SIRS, which show similar early symptomology. Endotypes offer an insight into the specific molecular dysregulation occurring, enabling specific prognostic markers and therapeutic options to prevent deterioration.

[00153] We hypothesized that robust gene expression endotypes existed within suspected sepsis patients that are associated with disease severity and outcomes. Accordingly, a multi-cohort blood RNA-Seq study was performed on patients at first clinical presentation for whom the physician suspected the possibility of sepsis. Initial analyses to identify stable

clusters of patients with similar transcriptomic profiles (endotypes) were performed with a cohort of 115 patients suspected of sepsis at first clinical presentation (within 2 hours of ER admission), originating from collaborating ERs in Netherlands and Canada (Table 1).

[00154] At the time of sampling, within two hours of emergency room (ER) admission, their quick Sequential Organ Failure Assessment (qSOFA) scores, which provided an early assessment of organ failure, tended to be modest, and as a cohort these patients demonstrated a full range from mild to relatively severe (range 0-3). Examining the demographic and clinical parameters of these patients (Table 1), the average age was 60 years (range 20-96), average SOFA scores measured 24 and 72 hours post admission were 2.0 ± 0.18 (range 0-10) and 1.0 ± 0.20 (range 0-11) respectively, and the average length of hospital stay was 8.1 days. Hospital mortality was relatively moderate at 13.9%, cf. the global mortality of 23% in sepsis [Rudd et al., 2020], consistent with the concept that around 50% of patients with prospective sepsis are subsequently found to have acquired more severe sepsis. The clinical heterogeneity observed within the cohorts exemplifies the need to accurately triage and prognosticate suspected sepsis patients. Cluster validation metrics were used to identify the optimal k value for clustering, namely 5 clusters according to Consensus Cluster CDF (examining the Top 10%, 25%, 50%, 75% and 100% of DE genes), and the minimal set of genes that should be used as input to a clustering algorithm.

(b) The endotype model provides mechanistic signatures of early sepsis

[00155] Patients belonged to one of five clusters, with each cluster representing a mechanistically-distinct endotype. We characterized the dominant biological mechanisms of each endotype by comparison to a set of 4 healthy controls (FIG. 2). Specifically, differential expression analysis was performed followed by over-representation (enrichment) analysis of up- and down-regulated pathways using the Reactome pathway database. Based on this, clusters 1 to 5 were named Neutrophilic-Suppressive (NPS), Inflammatory (INF), Innate Host Defence (IHD), Interferon (IFN) and Adaptive (ADA) endotypes, each based on several enriched pathways.

[00156] The NPS endotype showed a large dysregulation of gene expression when compared to healthy controls (5,341 total; 2,573 up-regulated; 2,768 down-regulated). Upregulated genes were related to aspects of the immune system pathways, particularly neutrophil degranulation, IL-15 signaling, TRIF-mediated programmed cell death and adaptive immune pathways (FIG. 2). The INF endotype also showed a large dysregulation of gene expression compared to healthy controls (3,830 total; 2,035 up-regulated; 1,795 down-regulated). Upregulated pathways were to some extent related to those seen in the NPS endotype, however, there was

unique activation of the inflammatory NIK-NF κ B signaling pathways and ROS/RNS production and reduced activation of neutrophil degranulation pathways.

[00157] The IFN, ADA, and IHD endotypes collectively showed related gene expression trends, as indicated by principal component analysis, but also substantial differences. The IFN endotype showed 4,468 total (2,195 up-regulated; 2,273 down-regulated) dysregulated genes compared to healthy controls. The high expression of interferon- α , and - β signaling pathways was unique to this endotype. The ADA endotype showed substantial dysregulation of gene expression (3,227 total; 1,636 up-regulated; 1,591 down-regulated). The endotype was notable for upregulation of adaptive immune pathways. Furthermore, the endotype displayed the lowest number of neutrophils suggesting possible neutropenia and upregulation of lymphocytes (FIG. 3). Taken together, the IFN and ADA endotypes appeared to be the most immunocompetent or possibly less sick when compared to other endotypes. The IHD endotype showed the fewest dysregulated genes compared to the other endotypes (1,419 total; 721 up-regulated; 698 down-regulated). This endotype showed few enriched pathways, with the exception of neutrophil degranulation, complement cascade, and interleukin (IL) signaling.

[00158] A gene signature representing endotoxin tolerance/cellular reprogramming (CR; also referred to as the ET signature) that was predictive of the onset of severe sepsis and organ failure based on a retrospective meta-analysis of >600 patients and a modest clinical study of a cohort of 72 ER patients suspected of sepsis has been previously published (Pena OM, et al., 2014; see also: WO 2015/135071). The NPS, INF, and IFN endotypes showed similar fold changes with respect to the CR signature, but the NPS endotype had slightly higher fold changes, indicative of immunosuppression and poor outcomes.

[00159] Based on clinical data (Table 2), the NPS and INF endotypes tended to be associated on average with more severe disease based on breathing difficulty (FIO₂) in the ER, hospital stay days, SOFA scores, blood culture and use of antibiotics, ICU admission, and increased risk of organ failure within 28 days of hospital admission (Table 2: FIG. 4). However, individual patients in each endotype had broadly different outcomes that could have been explained in part by the timeliness of appropriate treatment and other unknown variables. Using either Kruskal-Wallis or Chi square tests of significance, we determined endotypes were significantly associated with SOFA scores ($p=0.00093$), hospital stay duration ($p=0.0017$), ER FIO₂ (0.0077), blood culture (0.0040), blood lactate levels (0.034), and risk of organ failure within 28 days (0.0065). The clear associations between endotypes and clinical symptomology and

outcomes indicated that the endotypes represent a useful tool to prognosticate patients, while their underlying mechanistic differences indicate the potential for personalized therapy.

[00160] Subsequently gene expression signatures were identified by comparing global gene expression profiles between endotypes (top 200 differentially expressed genes when comparing each endotype to all others). This reflected the unique biological character of each endotype as revealed by plotting the gene expression differences onto protein:protein interaction (PPI) networks using NetworkAnalyst (FIGs. 5-9). The fact that, for each endotype, these unique genes form a coherent and well interconnected functional network indicates that they represent biologically meaningful clusters of genes, i.e. reflecting the underlying mechanisms of sepsis in the particular endotype. Darker coloured nodes (circles) represent genes from the signatures that are differentially expressed (DE), while light grey nodes are first order interacting and interconnecting nodes, while lines represent known (curated) functional interconnections from the database InnateDB (<https://www.innatedb.ca/>; Breuer et al., 2013). DE genes between endotypes were then used as input to a machine learning algorithm to obtain a signature that could be used to predict endotype status in a patient. Specifically, we derived a multinomial LASSO regularized regression to derive reduced gene sets to classify patients. This revealed that our signatures were very accurate in predicting endotypes with an Area under the receiver operating curve (AUC, a surrogate for accuracy, of 98%; Sensitivity of 80%; Specificity of 96%). There were 88 genes selected, which represents an effective signature to classify patients into endotypes (Table 3). These genes showed clear expression patterns with respect to the endotypes, indicating a moderate set of genes accurately differentiating each endotype (FIG. 10). Another 247 genes also showed clear expression patterns with respect to the endotypes (Table 4). In Tables 3 and 4, genes are bolded and arranged according to the endotype that they assist in classifying.

[00161] As can be clearly seen from Tables 3/4, most of these genes had high over-expression in one endotype (relative to individuals without sepsis) and either no increase or a decrease (i.e., negative fold changes) in expression in the other 4 endotypes. We examined for overlapping genes between our 88 gene signature and published literature on sepsis signatures. Generally, there was little overlap. Thus Maslove et al. (2012) described a 170 gene signature with only 2 overlapping genes (ARG1, ANXA3), Scicluna et al. (2017) described a 140 gene signature with only 9 overlapping genes [PLEKHO1 (oppositely regulated), APOL1, RIOK3, BNIP3L, GADD45A, PFKFB2 (not endotype specific), EPSTI1,

SERPING1, GLRX5], while Sweeney et al. (2018) described a 33-gene signature with only 3 overlapping genes [PLEKHO1, GADD45A (oppositely regulated), ARG1]. Thus, the literature is ambiguous about genes PLEKHO1, GADD45A and PFKFB2. Furthermore, these studies looked at much later stage patients (already in the ICU) at which time sepsis is much easier to predict, and they also relied on microarray data which is considerably less accurate, and these studies were generally much smaller than ours. Critically it has been shown that at the time of first clinical presentation (in the ER) for every hour's delay in applying appropriate treatment there is a 7.6% increased risk of death from sepsis (Kumar A et al. Crit Care Med 2006; 34:1589–1596), so it is clear that these studies were looking at too late a time to provide meaningful clinical input that would impact strongly on treatment. Thus, it is perhaps not surprising that the endotypes described in those papers do not correspond in any simple fashion to the endotypes described in this patent application.

[00162] To try to reduce the size of signatures, we also tested whether the expression of pairs of genes from Tables 3/4 had diagnostic potential when predicting a specific endotype, compared to all others, by using logistic regression (e.g. 24 NPS DE genes led to 276 unique gene pairs tested). The data in Table 5 shows a broad range of gene pairs with excellent accuracy (expressed as Area under the Curve of Receiver Operating Characteristics, AUCROC or AUC), as well as testing Sensitivity (true positive rate) and Specificity (true negative rate). AUC helps one to visualize how well a machine learning classifier is performing, thus providing an estimate of accuracy. Sensitivity is the true positive rate (i.e., what proportion of the positive class got correctly classified) and Specificity is the true negative rate (i.e., what proportion of the negative class – in this case all other endotypes or rest - got correctly classified). The results are expressed as a fraction of 1 but can be considered equivalent to a percentage when multiplied by 100. Overall the range of AUC accuracy was 86.1-98.8%, with Sensitivity of 74.1-97.5%, and Specificity of 75.6-92.4%. Table 6 includes data from an expanded list of gene pairs that classify into specific endotypes when compared to all others. ROC/Accuracy, Sensitivity and Specificity are expressed as percent. It is thus clear from the results herein that these gene pairs, and predictably many of the genes in Tables 3/4 assessed as singles, pairs or other multiples, represent a highly effective method of classifying patients into endotypes, while they are still in the emergency ward.

(c) Different mechanisms and comparison with the literature

[00163] Looking at the previous section, using consensus clustering we were able to test the hypothesis that robust mechanistically-distinct clusters exist within suspected sepsis patients. To confirm that each cluster represents clinically relevant-endotypes, we determined that the clusters were associated with clinical severity and outcomes. The endotype model stratified patients into one of five endotypes, each with a unique gene expression profile exhibiting diverse molecular responses. This has a very important implication. There are very few effective treatments for sepsis and to date our limited understanding of the mechanisms involved have limited the development of disease specific treatments. For example, more than 30 trials with different agents for suppressing the early hyper-inflammatory (cytokine storm) response in sepsis patients failed largely because of the different underlying mechanisms involved. To enable the development of personalized medicines for sepsis it is desirable to be able to understand the underlying mechanisms in subgroups (i.e., endotypes) of patients.

[00164] The five endotypes had diverse transcriptional profiles, with substantial heterogeneity observed in the innate, adaptive, and cytokine signaling pathways, and others (FIG. 2). The NPS and INF endotypes were associated with higher SOFA scores, longer hospital stays, and mortality among others (FIGs. 4, 13). In the ER cohort, the NPS and INF endotypes showed different cytokine signaling profiles and varying expression of the CR and inflammatory gene signatures, indicating the NPS endotype displayed a more immunosuppressive profile (FIG. 4). Studies indicate neutrophils do have paradoxical roles in sepsis, wherein their first-line host defences are beneficial, but when over-stimulated or reprogrammed contribute to organ dysfunction [Sônego F, et al. *Frontiers in Immunology*. 2016;7:155. doi:10.3389/fimmu.2016.00155]. While not wishing to be limited by theory, this suggests neutrophil reprogramming may indeed be occurring, with the NPS and INF endotypes displaying varying states of reprogramming.

[00165] The other three endotypes demonstrated distinct and novel mechanisms, and tended to cluster on PCA while demonstrating significantly lower ER SOFA scores, and several other clinical parameters. Of these the ADA endotype was associated with substantially younger patients who showed down-regulation of the predictive CR signature, rapid resolution of SOFA scores, higher predicted levels of lymphocytes and upregulation of B-cell pathways, and was not identified in ICU patients. The IFN and ADA endotypes displayed the overall best prognoses, and less severe clinical symptomology (e.g., lower SOFA scores) and outcomes, cf. other endotypes.

[00166] The IFN endotype was particularly marked by an elevated expression of interferon signaling pathways. Intriguingly as shown below, in ICU patients, this endotype was associated with Covid-19 positivity. Thus, while not wishing to be limited by theory, the concerted interferon response could reflect a viral etiology [Li, H., et al. The Lancet, 2020;395:1517-1520], or reflect strong inflammatory/anti-viral responses rather than immunosuppression that dominates in severe sepsis.

[00167] To the best of our knowledge, there are three studies which have explored endotypes in adult sepsis, and which have also analyzed associated clinical characteristics [Scicluna BP et al, 2017; Davenport EE, et al. 2016; Maslove DM, et al. 2012]. These studies looked at much later stage patients [already in the ICU] at which time sepsis is much easier to predict and relied on microarray data which is considerably less accurate and these studies were generally much smaller than ours. However, it has been shown that at the time of first clinical presentation [in the ER] for every hour's delay in applying appropriate treatment there is a 7.6% increased risk of death from sepsis, so it is clear that these studies were looking at too late a time to provide meaningful clinical input that would impact on treatment. Nonetheless, we were interested in comparing the endotypes our group identified to the ones previously published. Maslove *et al.* [2012] specifically profiled neutrophil gene expression to identify endotypes. They uncovered two endotypes, namely Subgroup1 and Subgroup 2. Subgroup 1 was associated with higher severity scores, and increased expression of key inflammation pathways in neutrophils, specifically, cytokine signaling pathways and Toll-like receptor (TLR) signaling. This study is consistent with our findings, which showed an even earlier role of neutrophils. Davenport *et al* [2016] identified the Sepsis Response Signature 1 (SRS1) and Sepsis Response Signature 2 (SRS2) endotypes, with SRS1 associated with higher mortality. Similarly, the high mortality Mars1 endotype of Scicluna *et al* [2017], concluded on the basis of the reduced expression of TLR signaling, NFkB signaling, T cell receptor activity, and several metabolic pathways, that the endotype displayed hallmarks of immunosuppression. In our data, NPS, INF, and IHD endotypes all displayed hints of immunosuppression, and were evident in the ICU cohort. But most notably, the cellular underpinnings for these three endotypes are different from any previously described study. Whereas we identified neutrophils associated with immunosuppressed endotypes, the SRS and Mars endotypes were not associated with altered neutrophil proportions. The endotypes we identified deviate from several endotype models previously published by displaying a clear role of neutrophils in sepsis progression. Nevertheless, the

evidence of immunosuppression in more severe patients is definite, regardless of cellular origin but the details seem to differ across these different studies and our study. This indicates endotypes characterizing suspected sepsis patients likely uncover some related patterns, which emphasizes the feasibility of identifying and prognosticating sepsis at first presentation to the ER and ICU, but also discrete differences suggesting that not all signatures have equal value.

(d) ICU patients including those with severe Covid-19 infections retained endotypes

[00168] The presence of these mechanistically and clinically relevant sepsis endotypes were validated in a sub-cohort of 82 critically ill patients (Table 1) enrolled in the COLOBILI study (St. Michael's Hospital, Toronto). Patients had severe respiratory failure and suspected pulmonary sepsis on day-0/1 of ICU admission; of these PCR on nasopharyngeal and/or endotracheal tube aspirates confirmed SARS-CoV-2 RNA in 27 patients. This cohort demonstrated higher severity and poorer outcomes when compared to the ER cohorts (24% mortality cf. 14%).

[00169] A Mechanistic endotype classifier was applied to predict endotype status using 88 genes from Table 3, and Gene-Set Variation Analysis was used to measure the enrichment of the five endotype signatures (FIG. 11). The model classified ICU patients into 4 endotypes with most (84%) fitting into the more severe NPS/INF endotypes. The ADA endotype was not identified, consistent with the observed downregulation of adaptive immune processes in later-stage sepsis patients. Interestingly, the IFN endotype was only found in 7/27 Covid-19 patients. The general trends in enriched pathways defining each endotype were recapitulated in the ICU (FIG. 12), when compared to the ER (FIG. 2), patients. In general, pathway trends were similar to those observed in the ER patients, with the exception of Neutrophil degranulation, which was enriched in NPS, INF, and IHD patients. While not wishing to be limited by theory, this may reflect the increased severity in ICU patients. The NPS and INF endotypes showed the worst prognosis, with higher 24-hour SOFA scores (mean 7.9 ± 0.6 ; $p=0.0035$) (Table 7; FIG. 13), while the NPS endotype displayed substantially higher 28-day mortality when compared to the INF endotype. No patients from the IHD or IFN endotypes died. This indicated the IFN endotype reflected a robust/effective interferon response, while the IHD endotype might generally reflect less severe patients.

[00170] The patients in the ICU cohort were severely ill patients with suspicion of Covid-19. Final confirmation of Covid-19 positive infections was determined using multiple PCR analyses, resulting in a determination of 27 positive and 55 negative patients. Comparing gene expression profiles between SARS-CoV2 positive and negative patients demonstrated 1,221

DE genes (663 up; 558 down). As previously demonstrated [Sadanandam A et al. *Cell Death Discov.* 2020; 6, 141], interferon α , β , and γ pathways, as well as NOTCH, RHO GTPases, WNT signaling pathways and platelet signaling pathways were upregulated in Covid-19 patients when compared to negative patients (FIG. 14, top left). Interferon pathways were also upregulated in non-Covid ICU patients, but Covid-19 positive patients demonstrated a relatively much larger increase in these and other anti-viral pathways. Importantly, Covid-19 patients grouped generally with other ICU patients in terms of endotype assignment (FIG. 14, right); this confirmed later stage Covid-19 patients generally display the same molecular responses as sepsis patients [Prescott HC, Girard TD. *JAMA* 2020; 324.8:739–740. doi:10.1001/jama.2020.14103]. Intriguingly the IFN endotype was identified only in Covid-19 patients and, although no patients were assigned to the Adaptive endotype by the endotype classifier, both the IFN and ADA endotype signatures were generally enriched in PCR-positive patients. While not wishing to be limited by theory, this likely reflected cellular immune system alterations in Covid-19 patients. Thus, it is evident that the molecular responses governing each endotype reflect markers of severity, and are generally applicable to patients with all-cause sepsis, including Covid-19 sepsis. Of note, no patients assigned to the IFN endotype died, which, while not wishing to be limited by theory, might suggest this endotype identified patients with viral infections moderated by effective anti-viral responses, and better prognoses.

[00171] An objective was to further validate our endotypes in ICU patients presenting with severe sepsis. Given the current pandemic, we had the unique opportunity to recruit ICU patients suspected of Covid-19. This allowed us to determine whether our endotypes were applicable to severe ICU patients, Covid-19, and more generally to sepsis patients with viral infections. We first examined the major gene expression differences between severe ICU patients and ER patients suspected of sepsis. It was evident that adaptive immune pathways were downregulated compared to the situation in suspected sepsis (ER) patients and healthy controls. It is discussed in the literature that severely sick septic patients typically display a suppressed adaptive immune system, or more generally immunosuppression, featuring T cell exhaustion, lymphocyte apoptosis, and diminished cytotoxicity [Hotchkiss et al. 2013]. When classifying patients into endotypes, we observed that there were no ADA endotype patients. Considering adaptive immune processes were downregulated, this explains the observation. Mortality was much more likely in the NPS and INF endotypes. Considering severely ill sepsis patients feature robust signals of immunosuppression, it seems likely that the NPS endotype captures this phenotype. Taken together, the cohort showed us that early signatures of SIRS and

sepsis are applicable to severely ill patients collected within the first day of ICU admission and early changes appear to persist through early sepsis and SIRS to full blown sepsis.

[00172] The patients within the ICU cohort were suspected of Covid-19, and this constituted part of the inclusion criteria. Therefore, we also had the opportunity to explore differences between Covid-19 positive and negative patients, especially in the context of all cause sepsis endotypes we identified in ER patients. Functional enrichment showed Type I and II Interferon related pathways were upregulated in Covid-positive patients. This has been observed in previous literature exploring Covid-19 [Prescott HC, and Girard TD, 2020], and generally observed in viral infections given the role interferons play in curbing virus translation. Generally, the Covid-19 patients did not exclusively fall into one endotype, although most Covid-positive patients showed upregulation of the IFN (and ADA) signature. This may indicate the Interferon signature may be useful to identify viral infections. Many studies show that Covid-19 patients display evidence of excessive and dysfunctional neutrophils [Parackova Z et al. Cells. 2020;9(10). doi:10.3390/cells9102206]. Considering the endotypes discovered reflect the same processes, it is evident the neutrophilic role in infection applies generally to severity and disease outcomes.

(e) Supervised analysis of SOFA-based severity groups displayed signatures not fully captured by endotypes

[00173] In general patients within the NPS and INF endotypes progressed to poorer outcomes when compared to the IHD, IFN, and ADA endotypes. However, for some patients the predicted prognoses were not accurate based on actual patient SOFA scores (an assessment of organ failure), ICU admission, and mortality. While not wishing to be limited by theory, this might reflect rapid treatments like antibiotics to prevent further progression, genetic background or existing conditions that could influence deterioration. We explored whether there were early gene expression differences between patients in High (SOFA scores ≥ 5), Intermediate (SOFA ≥ 2 and < 5), and Low (SOFA < 2) severity groups (measured 24 hours after admission), representing signatures of severity. To capture the full range of severity observed, patients within the ER cohort and ICU cohort were included. Specifically, High severity patients (n=60) progressed to SOFA scores greater than or equal to five assuming baseline scores of zero; Intermediate severity patients progressed to SOFA scores between two and five (n=67); Low severity patients progressed to SOFA scores between zero and one (n=67). We identified DE genes by comparing each group to the healthy controls (n

= 9), followed by pathway enrichment (FIG. 15). There were 359 (336 up-regulated; 23 down-regulated), 2297 (1266 up-regulated; 1031 down-regulated), and 2068 (1333 up-regulated; 735 down-regulated) when comparing the Low, Intermediate, and High severity groups to healthy controls, respectively. The 157 genes that showed a pattern of differential expression in the more severe cf. less severe patients is shown in Table 8. A reduced 73 gene set was obtained by LASSO regularization (* in Table 8).

[00174] Using the various sets of DE genes, the hypothesis-based CR signature and an 8-gene sub-signature, we trained classification models predictive of severity group (Table 9). Specifically, logistic regression (with LASSO regularization) was used to predict High vs. Low (represented the extreme phenotypes) and High + Intermediate vs. Low severity groups. The models predicting High vs. Low severity groups performed quite well across the training and test sets, which did not include patients with Intermediate severity. The models predicting High/Intermediate patients vs. Low severity groups performed fairly and were comparable or better than models published by other groups that were trained on often questionable sepsis proxies like blood culture and clinician diagnoses rather than SOFA-based severity.

[00175] These data show that a six gene sub-signature, CCL4L2, GPR84, HRK, MMP8, GGT5, RASGRF1, selected from those genes in Table 8, was capable of accurately predicting severity as early as the first clinical presentation in the emergency room, and did this almost as effectively as the entire set of DE genes.

[00176] While the disclosure has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the disclosure is not limited to the disclosed examples. To the contrary, the present disclosure is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

[00177] All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

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Table 1: Sepsis severity and outcomes of patients included in the endotype discovery and validation cohorts*.

Parameter	ER Cohort (N= 115)	ICU Cohort (N=82)
Age (years)	59.9 ± 1.5	61.7 ± 1.7 (82)
Sex (% Female)	43.5% (50/115)	30.5% (25/82)
Location(s)	Groningen, Netherlands (90%); Vancouver, Canada (10%)	Toronto, Canada (100%)
Duration of illness before ER/ICU arrival (days)	4.2 ± 0.51	6.6 ± 1.07 (47)
ER qSOFA score	0.9 ± 0.08	Not applicable
ER/ICU 24H SOFA score	2.0 ± 0.18	7.7 ± 0.63 (60)
ER/ICU 72H SOFA score	1.0 ± 0.2	7.8 ± 0.65 (54)
Hospital/ICU stay (days)	6.2 ± 0.74	11.8 ± 1.1 (63)
Blood Culture Positive (%)	21% (24/112)	14.3% (9/63)
ICU Admission	9.6% (11/115)	98% (80/82)**
Mortality	13.9% (16/115)	24.4% (20/82)
SARS-CoV-2 PCR Positive	Not Available: Pre-pandemic	32.9% (27/82)

* The mean value, standard deviation, and total observations used are presented for numerical variables, i.e. mean ±SE (total observations when not equal to the size of the cohort). Categorical variables are presented as total positive observations, percent, and total observations, i.e. total % positives (of total observations).

** 2 patients collected from ward.

Table 2: Clinical data of patients belonging to endotypes in the discovery ER cohorts*.

Parameter	Mechanistic Endotypes					P Value
	NPS (N=16)	INF (N=34)	IHD (N=16)	IFN (N=15)	ADA (N=34)	
ER qSOFA	1.3 ± 0.2	1.0 ± 0.1	0.9 ± 0.2	1.3 ± 0.2	0.5 ± 0.1	9.3e-4
Hospital Stay (days)	10.7 ± 1.9	8.3 ± 2.1 (33)	4.4 ± 1.1	4.7 ± 0.8	3.5 ± 0.6	1.7e-3
Blood Culture Result	53.3% (8/15)	26.5% (9/34)	6.2% (1/16)	26.7% (4/15)	6.2% (2/32)	0.0040
ER FIO ₂ (%)	28.4 ± 5.0 (15)	26.7 ± 1.7	22.5 ± 1.0 (15)	23.4 ± 1.2	21.3 ± 0.3	0.0077
Sex, female	81.2% (13/16)	41.2% (14/34)	31.2% (5/16)	20% (3/15)	44.1% (15/34)	0.0080
Treatment - O ₂ Therapy	62.5% (10/16)	41.2% (14/34)	31.2% (5/16)	46.7% (7/15)	14.7% (5/34)	0.011
Treatment – Antibiotics	87.5% (14/16)	82.4% (28/34)	81.2% (13/16)	66.7% (10/15)	52.9% (18/34)	0.022
ER Urea (mmol/L)	8.5 ± 0.8	8.3 ± 1.3 (33)	10.5 ± 1.3	8.5 ± 0.85	6.8 ± 0.7	0.026
ER Lactate	2.5 ± 0.5 (14)	1.8 ± 0.2 (26)	1.4 ± 0.1 (12)	1.4 ± 0.2 (12)	1.3 ± 0.1 (20)	0.034
ER Systolic (mmHg)	113.1 ± 4.74	130.7 ± 4.09	137.6 ± 5.85	124.2 ± 6.83	129.6 ± 3.01	0.045
ICU Admission	25% (4/16)	14.7% (5/34)	0% (0/16)	6.7% (1/15)	2.9% (1/34)	0.056
ER Respiratory Rate (breaths/min)	21.8 ± 1.5 (16)	22.8 ± 1.6 (33)	23.2 ± 1.4 (15)	23.8 ± 1.3 (14)	19.3 ± 0.9 (28)	0.061
Age	60.1 ± 4.9	63.7 ± 3.0	66.2 ± 3.5	59.3 ± 6.0	53.4 ± 3.1	0.085
ER MAP (mmHg)	97.7 ± 5.0	109.5 ± 3.3	115.5 ± 4.8	104.5 ± 5.4	111.9 ± 2.9	0.089
ER SOFA Score	2.2 ± 0.4	2.4 ± 0.4	2.0 ± 0.5	1.9 ± 0.4	1.4 ± 0.3	0.15
ER Diastolic (mmHg)	73.6 ± 4.3	74.8 ± 2.3	76.3 ± 4.8	69.8 ± 3.7	80.4 ± 2.2	0.17
ER Temperature (Celsius)	37.9 ± 0.32	37.8 ± 0.17	37.5 ± 0.2	38.2 ± 0.24	37.8 ± 0.16	0.29
Within 72 SOFA	1.4 ± 0.56	1.3 ± 0.44	0.5 ± 0.18	1.1 ± 0.6	0.7 ± 0.31	0.29
Readmit Within 28 Days	26.7% (4/15)	17.6% (6/34)	18.8% (3/16)	0% (0/14)	24.2% (8/33)	0.36
ER Creatinine (mg/dl)	99.5 ± 10.9	94.5 ± 6.1	114.4 ± 10.8	117.9 ± 14.7	105.7 ± 19.0	0.36
ER Aspartate amino-	33 ± 4.5	38.6 ± 5.7	41.1 ± 10.7	30.5 ± 8.0	33.4 ± 3.96	0.37

transferase (U/L)			(15)			
ER Alanine Amino transferase (IU/L)	32.7 ± 4.79	43.6 ± 6.08	31.6 ± 5.31 (15)	36.1 ± 11.31	36.6 ± 4.1	0.41
ER Alkaline phosphatase (U/L)	127.9 ± 16.0	169.5 ± 38.8 (33)	119.6 ± 19.0 (14)	90.9 ± 10.1	187.4 ± 52.3 (32)	0.45
Duration of Illness Prior to ED Arrival	4.2 ± 1.1	4.1 ± 1.1	3.1 ± 0.5	3 ± 1.3	5.3 ± 1.1	0.47
ER Bilirubin (mg/dl)	13.3 ± 1.5	15.8 ± 2.8 (33)	13.6 ± 2.1 (14)	14.1 ± 2.1	14.8 ± 3.4 (31)	0.55
ER GGT Gamma-Glutamyl Trans-peptidase (IU/L)	97.5 ± 20.4	165.6 ± 43.9 (33)	123.8 ± 64.0 (14)	81.8 ± 17.9	134.4 ± 33.9 (32)	0.55
Readmit Within 6 Month	38.5% (5/13)	38.7% (12/31)	20% (3/15)	21.4% (3/14)	25.8% (8/31)	0.58
On Antibiotics Prior to ER Arrival	25% (4/16)	32.4% (11/34)	25% (4/16)	13.3% (2/15)	26.5% (9/34)	0.77
ER Altered Mental State	18.8% (3/16)	17.6% (6/34)	12.5% (2/16)	20% (3/15)	8.8% (3/34)	0.81
ER Heart Rate (beats/min)	105.6 ± 5.5	103.8 ± 3.5	98.5 ± 3.7	104.3 ± 4.8	100.5 ± 2.9	0.87
Mortality	12.5% (2/16)	14.7% (5/34)	12.5% (2/16)	13.3% (2/15)	14.7% (5/34)	1

* The mean ± standard error, and total available observations for numerical variables (N only indicated for total available observations when not equal to total number of patients in the endotype). Categorical variables are presented as percent positive (total positive/total available observations). P values derived from Kruskal-Wallis and Chi square tests testing for significant differences between endotypes for numerical and categorical values, respectively.

Table 3: LASSO selected genes for endotype classification*.

Gene	Description	Fold Change (FC)				
		NPS	INF	IHD	IFN	ADA
KLF14	Kruppel like factor 14	14.45	-1.56	-3.39	-3	-16.31
HPGD	15-hydroxyprostaglandin dehydrogenase	9.9	-1.57	-3.49	-1.03	-9.65
PCOLCE2	procollagen C-endopeptidase enhancer 2	9.21	-1.39	-3.01	-1.35	-11.56
SLC51A	solute carrier family 51 subunit alpha	8.87	-1.35	-7.55	1.17	-17.26
OLAH	oleoyl-ACP hydrolase	8.8	-1.43	-4.18	-1.07	-11.82
TNFAIP8L3	TNF alpha induced protein 8 like 3	8.31	-1.06	-2.81	-1.24	-14.93
EFNA1	ephrin A1	8.1	-1.37	-2.21	-1.87	-3.9
ZDHHC19	Zinc finger DHHC-type palmitoyltransferase	8.03	-1.01	-7.14	1.16	-9.72
GPR84	G protein-coupled receptor 84	7.31	1.02	-5.93	-1.08	-9.14
ORM2	orosomucoid 2	7.11	1.33	-2.65	-1.02	-10.13
ARG1	arginase 1	5.4	1.05	-1.74	-1.09	-7.91
ATP9A	ATPase phospholipid transporting 9A (put.)	4.68	1.21	-2.61	1.14	-7.49
PFKFB2	6-phosphofructo-2-kinase	4.22	-1.01	-2.65	1.81	-9.23
NSUN7	NOP2/Sun RNA methyltransferase FM 7	4.01	1.12	-2.3	1.28	-5.47
GADD45A	growth arrest & DNA damage inducible α	3.89	1.22	-1.93	1.09	-5.64
ANXA3	annexin A3	3.27	-1.05	-2.61	2.05	-3.99
ILCR1	interleukin 1 receptor type 1	3.18	1.1	-1.62	1.18	-3.35
MLLT1	MLLT1 super elongation complex subunit	3.11	-1.13	-2.03	1.39	-2.26
MIR646HG	MIR646 host gene	2.79	1.2	-1.27	1.05	-3.03
AGFG1	ArfGAP with FG repeats 1	2.73	-1.07	-1.51	1.58	-2.84
KREMEN1	kringle containing transmembrane protein 1	1.92	1.03	-1.81	1.84	-2.06
BNIP3L	BCL2 interacting protein 3 like	-1.47	3.19	-1.55	-1.81	-2.29
RIOK3	RIO kinase 3	-1.56	3.19	-1.42	-1.61	-2.48
TSPAN5	tetraspanin 5	-1.59	3.56	-1.61	-1.96	-2.48
GLRX5	glutaredoxin 5	-1.81	4.14	-1.9	-2.16	-2.64
TSPO2	translocator protein 2	-2.07	6.82	-2.45	-2.21	-2.39
TLCD4	TLC domain containing 4	-2.08	4.52	-1.68	-2.05	-3.16
SPTA1	spectrin alpha, erythrocytic 1	-2.7	3.66	-1.16	-1.82	-2.51
RHCE	Rh blood group CcEe antigens	-2.8	6.76	-2.02	-2.74	-1.98
THEM5	thioesterase superfamily member 5	-2.87	9.38	-3.9	-2.87	-3.23
FAM83A	family with sequence similarity 83 FM A	-3.09	9.87	-3.72	-18.01	-11.3
FECH	ferrochelatase	-3.2	6.85	-2.09	-4.08	-3.66
GYPA	glycophorin A (MNS blood group)	-4.37	10.03	-1.32	-5.01	-2.92
CA1	carbonic anhydrase 1	-4.81	10.56	-2.95	-5.16	-7.89
IFIT1B	IFN-induced prot, tetratricopeptide repeats	-5.14	7.39	-3.25	-3.29	-2.7
SLC6A19	solute carrier family 6 member 19	-5.99	27.78	-2.6	-9.18	-10.2

RNF182	ring finger protein 182	-4.19	7.2	-1.9	-2.16	-4.34
SDC2	syndecan 2	1.37	-1.28	2.81	-2.28	-1.72
LPL	lipoprotein lipase	1.33	1.46	4.57	-1.35	-2.68
GRAMD1C	GRAM domain containing 1C	-1.01	1.08	1.8	-1.27	-1.5
MAP7	microtubule associated protein 7	-1.03	-1.56	1.84	-1.08	1
GPR34	G protein-coupled receptor 34	-1.03	-1.3	2.68	-1.2	-1.57
ABCA6	ATP binding cassette subfamily A member 6	-1.15	1.75	2.76	-1.6	-1.29
CACNA2D3	calcium voltage-gated channel aux. SU $\alpha 2\delta 3$	-1.18	-1.07	1.44	-1.54	1.12
SLC16A14	solute carrier family 16 member 14	-1.26	-1.22	3.18	-4.03	-1.21
PLCB1	phospholipase C beta 1	-1.3	-1.12	1.63	-1.72	1.14
TPRG1	tumor protein p63 regulated 1	-1.37	1.03	1.28	-1.66	1.19
DYNC2H1	dynein cytoplasmic 2 heavy chain 1	-1.47	-1.07	1.61	-1.62	1.09
MIR155HG	MIR155 host gene	-1.79	-1.25	2.95	-1.33	-1.32
ZNF600	zinc finger protein 600	-2.06	-1.09	1.44	-1.58	1.4
ALOX15	arachidonate 15-lipoxygenase	-2.36	-1.52	3.73	-3	-1.05
SPRED1	sprouty related EVH1 domain containing 1	-2.42	-1.1	2.83	-1.5	-1.26
TPPP3	tubulin polymerization promoting prot. FM3	-2.62	-1.24	1.25	-1.94	1.93
ADAM23	ADAM metallopeptidase domain 23	-3.03	1.07	1.43	-2.09	1.44
SMPD3	sphingomyelin phosphodiesterase 3	-4.12	-1.66	2.75	-2.43	1.53
SIGLEC8	sialic acid binding Ig like lectin 8	-5.01	-2.2	3.58	-3.16	1.51
ANKRD22	ankyrin repeat domain 22	1.28	-1.54	-4.83	4.49	-1.92
IFITM3	interferon induced transmembrane protein 3	1.13	-1.61	-3.69	2.46	1.17
PLEKHO1	pleckstrin homology domain containing O1	-1.64	-1.22	-1.25	1.03	1.63
APOL1	apolipoprotein L1	-2.51	-1.52	-2.79	3.23	1.27
TFEC	transcription factor (TF) EC	-2.51	-1.49	1.22	4.95	1.32
P2RY14	purinergic receptor P2Y14	-2.87	-1.62	-2.83	5.92	-1.53
BATF2	basic leucine zipper ATF-like TF-2	-2.89	-2.02	-5.53	4.84	1.26
CARD17	caspase recruitment domain FM 17	-3.04	-1.84	-2.41	5.76	-1.37
EPSTI1	epithelial stromal interaction 1	-3.09	-1.77	-2.96	2.91	1.62
ETV7	ETS variant transcription factor 7	-3.39	-2.06	-4.85	4.74	1.3
SERPING1	serpin family G member 1	-5.44	-2.56	-6.36	4.15	1.87
GBP5	guanylate binding protein 5	-7.65	-1.72	-2.81	4.59	1.16
RSAD2	radical S-adenosyl met. domain cont. 2	-10.26	-2.53	-6.26	3.31	2.23
IDO1	indoleamine 2,3-dioxygenase 1	-15.12	-3.25	-2.79	7.45	2.58
APOL4	apolipoprotein L4	-16.66	-1.72	-3.5	4.46	1.53
CD274	CD274 molecule	-2.36	-1.42	-3.22	4.77	-1.34
PDIA4	protein disulfide isomerase FM A 4	-1.11	-1.14	-1.17	-1.07	1.34
KIF14	kinesin family member 14	-1.32	1.19	-1.09	-1.01	1.01
CDC45	cell division cycle 45	-1.44	-1.04	-1.44	-1.94	1.91
GTSE1	G2 and S-phase expressed 1	-1.69	1.4	-1.66	-1.79	1.47
CCL2	C-C motif chemokine ligand 2	-1.7	-4.1	-7.56	-2.78	9.25
KIF15	kinesin family member 15	-2.23	1.34	-1.15	-1.47	1.32

CLEC4F	C-type lectin domain family 4 member F	-2.42	-3.96	1.23	1.73	3.68
LGALS3BP	galectin 3 binding protein	-2.8	-3.12	-3.45	1.33	4.16
KLHDC7B	kelch domain containing 7B	-3.17	-2.05	-1.84	-1.24	3.45
KCTD14	potassium channel tetramer domain cont. 14	-4.09	-7.29	-6.69	1.46	5.74
ISG15	ISG15 ubiquitin like modifier	-5.14	-3.77	-9.93	2.3	3.47
USP18	ubiquitin specific peptidase 18	-5.86	-4.75	-8.46	1.5	5.19
IFI27	interferon alpha inducible protein 27	-5.92	-1.58	-31.09	-1.02	4.01
SIGLEC1	sialic acid binding Ig like lectin 1	-7.74	-6.11	-5.66	1.6	5.29
OTOF	otoferlin	-22.51	-18.01	-17.31	1.22	13.7
CENPF	centromere protein F	-1.33	1.46	-1.39	-1.48	1.09

* These 88 genes represent a reduced signature that can be more readily translated for clinical use.

FM = family member. TF = transcription factor.

Table 4: Other markers based on highest gene expression in group of genes maximally differentiating each endotype from each other endotype.

Gene	Abbreviated Description	Fold Change (FC)				
		NPS	INF	IHD	IFN	ADA
HPGD	15-hydroxyprostaglandin dehydrogenase	9.9	-1.57	-3.49	-1.03	-9.65
ADAMTS3	ADAM metalloproteinase, thromb. type 1/3	6.55	-1.04	-2.43	1.18	-16.67
SEMA6B	semaphorin 6B	5.68	-1.04	-2.93	1.4	-7.97
NECAB1	N-terminal EF-hand Ca ²⁺ binding protein 1	6.02	1.33	-2.71	-1.07	-20.57
CD177	CD177 molecule	5.66	-1.08	-5.06	1.83	-13.12
IL1R2	interleukin 1 receptor type 2	5.92	-1.06	-5.13	1.35	-9.6
MMP9	matrix metalloproteinase 9	5.68	1.11	-3.17	-1.23	-5.94
EXOSC4	exosome component 4	5.45	-1.25	-3.69	1.13	-3.5
ENTPD7	ectonucleoside tri-Pi diphosphohydrolase 7	5.27	-1.16	-2.07	1.32	-6.03
RGL4	guanine nucl. dissociation stimulator like 4	5.13	-1.17	-2.71	1.28	-4.42
S100A12	S100 calcium binding protein A12	5.08	1.01	-2.8	1.27	-5.02
SPATC1	spermatogenesis and centriole associated 1	5.05	-1.08	-3.98	1.59	-7.3
DAAM2	dishevelled assoc. activator morphogenesis 2	5.03	-1.07	-2.58	1.21	-7.4
PI3	peptidase inhibitor 3	4.99	1.19	-1.65	-3.12	-2.68
OPLAH	5-oxoprolinase, ATP-hydrolysing	4.98	-1.11	-2.34	-1.02	-3.58
SPP1	secreted phosphoprotein 1	4.91	-1.57	-1.16	1.46	-4.52
PHF24	PHD finger protein 24	4.81	1.16	-1.78	-1.24	-4.88
FGF13	fibroblast growth factor 13	4.75	-1.57	-1.52	1.55	-4.65
XCR1	X-C motif chemokine receptor 1	4.69	-1.45	-1.45	1.12	-3.24
CYP19A1	cytochrome P450 family 19 subfam. A M1	4.6	1.21	-1.68	-1.05	-7.26
CYSTM1	Cys-rich transmembrane module cont. 1	4.52	-1.12	-3.81	1.62	-4.55
MCEMP1	mast cell expressed membrane protein 1	4.51	-1	-3.62	1.73	-6.83
GYG1	glycogenin 1	4.34	-1.03	-2.85	1.49	-4.72
FFAR3	free fatty acid receptor 3	4.25	-1.41	-5.23	1.47	-2.13
CA4	carbonic anhydrase 4	4.24	-1.02	-2.56	1.14	-3.58
GRB10	growth factor receptor bound protein 10	4.22	1.01	-2.03	1.19	-4.1
S100P	S100 calcium binding protein P	4.21	1.09	-2.19	1.27	-4.52
GALNT14	polypep N-acetylgalactosaminyltransferase	4.12	1.13	-2.6	1.14	-3.78
TMIGD3	transmembrane and Ig domain containing 3	4.1	-1.11	-1.56	1.09	-3.33
ALDH1A2	aldehyde dehydrogenase 1 FM-A2	4.01	-1.13	-2.26	1.17	-2.25
SYN2	synapsin II	3.91	1.01	-2.7	1.31	-3.23
KCNMA1	K ⁺ Ca ²⁺ -activated channel subfamily M α 1	3.89	-1.21	-2.79	1.26	-2.11
FSTL4	folliculin like 4	3.87	1.24	-1.44	-1.23	-3.86
IRAG1-AS1	IRAG1 antisense RNA 1	3.84	1.12	-2.7	1.41	-4.33
PFKFB3	6-phosphofructo-2-kinase	3.83	1	-2.53	1.62	-4.99
PDGFC	platelet derived growth factor C	3.82	-1.05	-1.2	1.06	-4.07
BTBD19	BTB domain containing 19	3.78	1.06	-3.69	1.54	-3.94

CST7	cystatin F	3.76	-1.03	-2.98	1.33	-2.95
ST6GALNAC3	ST6 NAG α -2,6-sialyltransferase 3	3.71	-1	-1.47	1.19	-3.97
NSMCE1-DT	NSMCE1 divergent transcript	3.71	1.15	-2.03	-1.19	-2.54
SOCS3	suppressor of cytokine signaling 3	3.67	-1.15	-3.53	2.12	-4.17
PLK3	polo like kinase 3	3.6	-1	-2.39	1.08	-2.43
ALPL	alkaline phos., biomineralization associated	3.57	1.18	-2.64	1.12	-3.24
PLIN5	perilipin 5	3.56	-1	-2.54	1.26	-2.81
SHROOM4	shroom family member 4	3.54	1.33	-1.53	1.01	-3.74
KCNE1B	K ⁺ voltage-gated channel SF E reg. SU1B	3.48	1.09	-3.28	1.31	-2.71
SLPI	secretory leukocyte peptidase inhibitor	3.43	-1.08	-1.36	-1.14	-2.16
ALOX5AP	arachidonate 5-lipoxygenase activating prot	3.43	-1.05	-2.65	1.37	-2.58
TMEM120A	transmembrane protein 120A	3.43	-1.09	-2.19	1.18	-2.27
IL1RN	interleukin 1 receptor antagonist	3.4	-1.56	-4.62	1.31	-1.95
AKR1C1	aldo-keto reductase family 1 member C1	3.38	1.12	-2.09	1.93	-5.34
CD163L1	CD163 molecule like 1	3.36	-1.29	-2	1.51	-2.29
GRAMD1A	GRAM domain containing 1A	3.35	1	-3.01	1.48	-2.8
PROK2	prokineticin 2	3.35	-1.06	-1.83	1.52	-3.4
UPP1	uridine phosphorylase 1	3.34	-1.08	-2.41	1.64	-3.15
ANKRD55	ankyrin repeat domain 55	3.3	1.24	-2.27	1.31	-4.13
TDRD9	tudor domain containing 9	3.29	1.04	-1.23	1.05	-3.41
CD82	CD82 molecule	3.26	1.03	-2.02	1.14	-2.47
ECHDC3	enoyl-CoA hydratase domain containing 3	3.24	1.03	-1.72	1.4	-3.51
MKNK1	MAPK interacting serine/threonine kinase 1	3.21	-1.06	-1.87	1.38	-2.8
POR	cytochrome p450 oxidoreductase	3.2	-1.09	-2.18	1.44	-2.57
AMPH	amphiphysin	3.19	1.04	1.03	-1.56	-2.67
DGAT2	diacylglycerol O-acyltransferase 2	3.18	-1.04	-1.92	1.24	-2.44
SPINK8	serine peptidase inhibitor Kazal type 8	3.15	1.2	-1.98	1.41	-3.45
BCL3	BCL3 transcription coactivator	3.14	1	-2.49	1.2	-2.15
ROM1	retinal outer segment membrane protein 1	3.14	-1.1	-1.67	1.38	-2.45
PLIN4	perilipin 4	3.09	1.16	-2.38	1.19	-2.77
SPDYA	speedy/RINGO cell cycle regulator FM A	3.08	1.25	-2.22	1.21	-2.57
MSRA	methionine sulfoxide reductase A	3.07	1.06	-1.82	1.01	-2.21
IL18RAP	interleukin 18 receptor accessory protein	3.06	-1.07	-2.67	2	-3.44
IER3	immediate early response 3	3.06	1.1	-1.91	1.19	-2.57
RFX2	regulatory factor X2	3	1.02	-1.66	1.14	-2.42
TSPO	translocator protein	3	1.01	-1.83	1.18	-2.25
TENT5C	terminal nucleotidyltransferase 5C	-2.86	5.73	-2.13	-3.21	-2.98
TSPAN7	tetraspanin 7	-2.27	5.44	-3.18	-3	-2.44
KANK2	KN motif and ankyrin repeat domains 2	-2.49	5.36	-1.9	-2.76	-3.13
RAP1GAP	RAP1 GTPase activating protein	-2	5.29	-3.4	-5.54	-2.29
SLC14A1	solute carrier Family 14/1 (Kidd blood gp)	-2.5	4.88	-1.63	-2.5	-3.04
HMBS	hydroxymethylbilane synthase	-1.63	4.83	-1.9	-2.04	-1.88

OSBP2	oxysterol binding protein 2	-1.75	4.79	-2.45	-3.31	-2.57
TFR2	transferrin receptor 2	-1.72	4.51	-1.91	-2.94	-2.04
TNS1	tensin 1	-2.08	4.51	-1.82	-2.53	-2.64
ALAS2	5'-aminolevulinate synthase 2	-1.72	4.42	-2.57	-2.78	-2.38
ARHGEF37	Rho guanine nucleotide exchange factor 37	-1.98	4.35	-1.71	-1.94	-2.89
KCNH2	K ⁺ voltage-gated channel SFM H/2	-1.62	4.29	-1.9	-3.39	-2.81
PTPRF	protein tyrosine phosphatase receptor type F	-1.85	4.29	-1.62	-1.73	-1.67
PRDX2	peroxiredoxin 2	-1.98	4.13	-2.23	-3.04	-1.96
ACKR1	Aty. chemokine receptor 1 (Duffy blood gp)	-1.87	4.05	-3.24	-2.89	-1.68
RHAG	Rh associated glycoprotein	-2.62	3.5	-1.56	-1.94	-2.22
TMCC2	transmembrane and coiled-coil domain F2	-2.47	6.73	-1.56	-2.7	-2.64
DYRK3	dual specificity Tyr phos. regulated kinase 3	-2.33	5.39	-1.61	-2	-2.2
ITLN1	intelectin 1	-2.82	5.62	-2.82	-2.97	-2.48
KLHDC8A	kelch domain containing 8A	-1.74	3.79	-1.74	-2.48	-2.18
AHSP	alpha hemoglobin stabilizing protein	-2.64	6.31	-3.21	-2.99	-3.07
GYPB	glycophorin B (MNS blood group)]	-3.29	6.07	-2.97	-3.74	-2.49
YPEL4	yippee like 4	-1.83	2.71	-1.32	-1.67	-1.96
CTSE	cathepsin E	-1.66	3.68	-2.23	-1.98	-3.18
ACHE	acetylcholinesterase	-1.79	4.64	-2.45	-3.05	-2.43
KLF1	Kruppel like factor 1	-2	5.3	-2.35	-3.12	-2.84
XK	X-linked Kx blood group	-2.68	5.39	-2.03	-3.05	-2.76
LRRC2	leucine rich repeat containing 2	-2.38	6.2	-2.18	-3.35	-3.47
HEPACAM2	HEPACAM family member 2	-2.59	4.16	-2.26	-2.52	-1.87
MAOA	monoamine oxidase A	1.44	3.6	-1.87	-3.67	-4.5
BPGM	bisphosphoglycerate mutase	-2.96	5.93	-2.27	-3.06	-3.04
SOX6	SRY-box transcription factor 6	-1.81	4.86	-2.12	-2.33	-3.21
BCAM	basal cell adhesion mol. (Lutheran blood gp)	-1.17	6.12	-3.15	-5.2	-6.58
ABCG2	ATP bind. cassette FM G/2 (Junior bld gp)	-2.79	4.76	-2.23	-1.99	-2.55
HEMGN	hemogen	-2.36	5.09	-2.19	-2.65	-2.8
RIPOR3	RIPOR family member 3	-1.28	2.8	-1.38	-1.85	-2.04
RHD	Rh blood group D antigen	-1.73	4.94	-2.65	-2.84	-2.71
SLC6A9	solute carrier family 6 member 9	-2.66	5.96	-2.32	-4.31	-3.78
KRT1	keratin 1	-1.95	4.49	-3.23	-2.44	-2.14
TRIM10	tripartite motif containing 10	-2.31	3.96	-1.72	-1.94	-2.28
SELENOP	selenoprotein P	-2.17	3.1	-1.11	-2.01	-1.92
SLC4A1	solute carrier FM 4/1 (Diego blood gp)	-2.33	5.04	-2.03	-2.74	-2.8
ERFE	erythroferrone	-1.32	4.31	-1.9	-5.73	-3.13
EPB42	erythrocyte membrane protein band 4.2	-2.08	4.99	-2.64	-2.99	-2.47
ANK1	ankyrin 1	-2.23	4.8	-1.86	-2.68	-2.73
SELENBP1	selenium binding protein 1	-1.93	4.99	-2.48	-2.84	-2.8
TMOD1	tropomodulin 1	-1.69	3.87	-2.03	-2.07	-2.41
SGIP1	SH3GL interacting endocytic adaptor 1	-1.91	3.8	-2.35	-2.47	-1.82

ATP1B2	ATPase Na ⁺ /K ⁺ transporting subunit beta 2	-1.87	3.02	-2.79	-1.57	-1.48
DNAJC6	DnaJ heat shock protein FM (Hsp40) C6	-3.21	4.74	-1.67	-2.83	-2.41
CR1L	complement C3b/C4b receptor 1 like	-1.59	3.71	-1.93	-1.73	-2.46
KEL	Kell metallo-endopeptidase (Kell blood gp)	-1.93	4.87	-2.66	-3.13	-3.09
SNCA	synuclein alpha	-2.12	4.69	-2.08	-2.59	-2.64
SLC2A1	solute carrier family 2 member 1	-1.54	4.36	-1.55	-1.98	-2.11
SPTB	spectrin beta, erythrocytic	-1.89	4.85	-2.05	-2.68	-2.98
RFESD	Rieske Fe-S domain containing	-2.98	3.6	-1.11	-1.98	-2.18
SEC14L4	SEC14 like lipid binding 4	-1.86	4.71	-1.98	-2.43	-2.84
CA2	carbonic anhydrase 2	-2.41	4.03	-1.45	-2.11	-2.44
ACSL6	acyl-CoA synthetase long chain FM 6	-3.61	3.97	-1.38	-3.03	-1.86
GMPR	guanosine monophosphate reductase	-1.58	3.94	-2.57	-2.41	-2.14
C1orf116	chromosome 1 open reading frame 116	-1.78	3.94	-1.82	-2.18	-2.37
PGF	placental growth factor	-6.52	3.91	-2.68	-1.09	-8.77
SFRP2	secreted frizzled related protein 2	-1.53	3.9	-2.08	-1.85	-2.47
SLC6A8	solute carrier family 6 member 8	-1.57	3.88	-1.91	-2.78	-2.25
BCL2L1	BCL2 like 1	-1.53	3.88	-2.17	-2.34	-2.32
GSPT1	G1 to S phase transition 1	-1.93	3.8	-1.77	-2.16	-2.22
SLC1A5	solute carrier family 1 member 5	-2.05	3.79	-1.86	-2.67	-1.89
RGS16	regulator of G protein signaling 16	-1.4	3.79	-1.6	-1.7	-2.32
AQP1	aquaporin 1 (Colton blood group)	-1.42	3.75	-1.87	-2.54	-2.37
BBOF1	basal body orientation factor 1	-1.64	3.75	-1.68	-2.02	-2.6
STRADB	STE20 related adaptor beta	-1.85	3.74	-1.84	-2.09	-2.23
RNF175	ring finger protein 175	-1.76	3.72	-1.63	-2.16	-2.23
CR1L	complement C3b/C4b receptor 1 like	-1.59	3.71	-1.93	-1.73	-2.46
MRC2	mannose receptor C type 2	-1.5	3.7	-1.82	-1.89	-2.44
ANKRD9	ankyrin repeat domain 9	-1.59	3.68	-2.22	-2.77	-1.91
MBNL3	muscleblind like splicing regulator 3	-1.92	3.64	-1.55	-2.12	-2.29
MXI1	MAX interactor 1, dimerization protein	-1.63	3.64	-1.62	-2.21	-2.42
DCAF12	DDB1 and CUL4 associated factor 12	-1.65	3.63	-1.68	-1.95	-2.45
NFIX	nuclear factor I X	-1.58	3.61	-2.18	-1.9	-2.13
RFESD	Rieske Fe-S domain containing	-2.98	3.6	-1.11	-1.98	-2.18
RBM38	RNA binding motif protein 38	-1.39	3.6	-1.72	-2.43	-2.41
MYL4	myosin light chain 4	-1.51	3.59	-2.73	-1.83	-2.03
FRMD4A	FERM domain containing 4A	-1.94	3.55	-1.57	-2.06	-2.05
ARHGEF12	Rho guanine nucleotide exchange factor 12	-2.05	3.54	-1.52	-1.87	-2.22
PLEK2	pleckstrin 2	-1.32	3.54	-1.85	-1.9	-2.64
MARCHF8	membrane associated ring-CH-type finger 8	-1.81	3.52	-1.72	-1.82	-2.22
FAM210B	family with sequence similarity 210/B	-1.4	3.46	-1.94	-2.31	-2.16
TRIM58	tripartite motif containing 58	-1.37	3.43	-1.84	-2.23	-2.23
DPCD	Deleted in primary ciliary dyskinesia hom.	-1.96	3.41	-1.78	-2.48	-1.72
UBB	ubiquitin B	-1.52	3.41	-2.23	-1.74	-2.11

SMIM5	small integral membrane protein 5	-1.44	3.34	-2.24	-1.8	-2.03
CLIC2	chloride intracellular channel 2	-2.59	3.34	-1.54	-1.41	-2.1
MFSD2B	major facilitator superfamily domain containing 2B	-1.27	3.3	-1.96	-2.41	-2.04
PBX1	PBX homeobox 1	-1.25	3.3	-1.91	-2.1	-2.24
ADD2	adducin 2	-1.69	3.29	-1.37	-2.34	-1.18
FAXDC2	fatty acid hydroxylase domain containing 2	-1.5	3.29	-1.82	-2.12	-1.97
ARL4A	ADP ribosylation factor like GTPase 4A	-1.77	3.28	-1.46	-1.3	-2.72
USP12	ubiquitin specific peptidase 12	-2.14	3.26	-1.25	-1.84	-2.19
EMID1	EMI domain containing 1	-1.13	3.25	-1.51	-2.38	-2.41
YBX3	Y-box binding protein 3	-1.54	3.24	-1.69	-2.09	-2.02
ISCA1	iron-sulfur cluster assembly 1	-1.68	3.24	-1.29	-2.07	-2.27
KLC3	kinesin light chain 3	-1.13	3.22	-2.01	-2.37	-2.11
KDM7A-DT	KDM7A divergent transcript	-1.39	3.16	-1.77	-1.94	-2.07
CTNNAL1	catenin alpha like 1	-1.38	3.16	-1.57	-2.28	-2.07
SLC7A5	solute carrier family 7 member 5	-1.02	3.16	-1.91	-2.26	-2.35
BLVRB	biliverdin reductase B	-1.46	3.14	-2.26	-1.61	-1.92
HBM	hemoglobin subunit mu	-1.31	3.13	-3.22	-1.97	-1.64
SIAH2	siah E3 ubiquitin protein ligase 2	-1.29	3.13	-1.87	-1.7	-2.23
RUNDC3A	RUN domain containing 3A	-1.34	3.12	-2.64	-2.45	-1.54
CISD2	CDGSH iron sulfur domain 2	-1.87	3.11	-1.53	-1.89	-1.87
PNP	purine nucleoside phosphorylase	-1.59	3.11	-1.67	-2.02	-1.87
DMTN	dematin actin binding protein	-1.31	3.11	-1.96	-2.02	-1.94
RGCC	regulator of cell cycle	-1.92	3.08	-1.55	-1.69	-1.86
TTC25	tetratricopeptide repeat domain 25	-1.32	3.08	-2.13	-1.68	-1.92
IGF2BP2	insulin like growth factor 2 mRNA binding protein 2	-1.41	3.08	-1.65	-2.1	-1.95
SLC22A23	solute carrier family 22 member 23	-1.41	3.04	-1.54	-1.7	-1.23
TAL1	bHLH transcription factor 1, erythroid differentiation factor	-1.31	3.04	-1.71	-1.96	-2.04
NUDT4	nudix hydrolase 4	-1.58	3.03	-1.19	-2.06	-2.24
ATP1B2	ATPase Na ⁺ /K ⁺ transporting subunit beta 2	-1.87	3.02	-2.79	-1.57	-1.48
ALDH5A1	aldehyde dehydrogenase 5 family member A1	-2.1	3.02	-1.41	-1.88	-1.74
PCDH1	protocadherin 1	-1.29	3.01	-1.6	-2.42	-1.88
PAGE2B	PAGE family member 2B	-1.18	3	-2.1	-1.61	-2.09
GPR82	G protein-coupled receptor 82	-1.23	-1.37	2.17	-2.27	1.12
PRSS33	serine protease 33	-3.13	-1.82	3.10	-2.22	1.36
IL5RA	interleukin 5 receptor subunit alpha	-2.87	-1.31	2.62	-1.65	1.14
TRIM2	tripartite motif containing 2	-1.69	-1.1	2.03	-2.45	1.11
TBC1D12	TBC1 domain family member 12	-1.87	-1.39	2.35	-1.33	1.03
ADGRD1	adhesion G protein-coupled receptor D1	-2.34	-1.01	2.34	-2.32	1.01
HDAC9	histone deacetylase 9	-2.38	-1.42	2.26	-1.56	1.28
PTGFRN	prostaglandin F2 receptor inhibitor	-2.05	-1.54	2.15	-1.32	1.24
PTGDR2	prostaglandin D2 receptor 2	-2.75	-1.3	2.06	-1.58	1.35
ANGPT1	angiopoietin 1	-1.3	1.3	2.05	-1.64	-1.66

KLHDC1	kelch domain containing 1	-1.73	-1.48	2.03	-2.01	1.3
EXOC3L1	exocyst complex component 3 like 1	-7.85	-2.5	-3.3	3.09	2.11
SEPTIN4	septin 4	-7.4	-2.85	-4.22	4.28	1.91
IRF7	interferon regulatory factor 7	-1.45	-2.18	-3.75	3.23	1.4
OAS1	2'-5'-oligoadenylate synthetase 1	-4.35	-2.39	-3.36	3	2
LY6E	lymphocyte antigen 6 family member E	-3.12	-3.61	-5.13	2.2	3.08
LAMP3	lysosomal associated membrane protein 3	-11.7	-2.67	-7.9	3.49	2.24
IFIT3	IFN induced protein, tetratricopeptide repts 3	-4.29	-2.04	-4.79	3.21	1.83
IFI44L	interferon induced protein 44 like	-8.03	-2.63	-4.63	3.4	2.12
TTC21A	tetratricopeptide repeat domain 21A	-2.44	-1.89	-1.84	1.15	2.65
SAMD4A	sterile alpha motif domain containing 4A	-10.03	-2.32	-1.49	1.3	3.16
SPATS2L	spermatogenesis associated serine rich 2 like	-4.28	-2.49	-3.13	2.29	2.51
HERC5	HECT&RLD, E3 ubiquitin protein ligase 5	-6.12	-2.09	-5.47	2.85	2.17
AGRN	agrin	-5.41	-2.27	-2.42	1.49	3.13
DHX58	DExH-box helicase 58	-3.35	-2.21	-2.97	2.21	2.3
TSHR	thyroid stimulating hormone receptor]	-1.88	1.01	-1.19	-3.88	2.18
TNFRSF13B	TNF receptor superfamily member 13B	-1.09	1.04	-1.49	-1.62	2.06
PARM1	prostate androgen-reg. mucin-like protein 1	-1.76	-1.16	-1.07	-2.21	2.02
FAM111B	family sequence similarity 111 member B	-2.92	-1.37	-1.39	-1.53	2.81
MCM10	minichromosome maintenance 10 repln. IF	-2.35	-1.13	-1.72	-1.51	2.4
LAG3	lymphocyte activating 3	-2.68	-1.07	-1.94	-1.3	2.2
CD38	CD38 molecule	-2.66	-1.45	-1.39	-1.07	2.34
IFNG-AS1	IFNG antisense RNA 1	-2.53	1.06	-1.28	-3.83	2.17
CDT1	chromatin licensing /DNA replication fact-1	-2.02	1.13	-1.44	-2.17	2.31
CDCA7	cell division cycle associated 7	-2.85	-1.15	-1.09	-1.54	2.01
EME1	Essential meiotic structure-spec. endonucl-1	-2.28	-1.25	-1.3	-1.4	2.15
CTLA4	cytotoxic T-lymphocyte associated protein 4	-2.48	-1.13	-1.13	-1.56	1.99
HES4	hes family bHLH transcription factor 4	-6.73	-2.53	-1.41	1.05	3.44
PACSIN1	PKC & casein kinase substrate in neurons 1	-2.69	-1.55	-1.62	-2.65	3.41
IL12RB2	interleukin 12 receptor subunit beta 2	-4.46	-1.4	-2.12	-1.59	3.23
IL4I1	interleukin 4 induced 1	-2.28	-1.82	-2.7	-1.12	3.17
P2RY6	pyrimidinergic receptor P2Y6	-2.44	-1.88	-1.89	-1.12	3.03
KIF19	kinesin family member 19	-4.68	-1.2	-1.05	-3.7	2.69
TMPRSS3	transmembrane serine protease 3	-3.53	-1.4	-1.43	-1.2	2.5

Table 5: Examples of diagnostic accuracy of pairs of endotype classifiers.

Comparison	Gene Pairs tested	Percent Accuracy (AUC-ROC), Sensitivity and Specificity of diagnosis		
		AUC	Sensitivity	Specificity
NPS vs. Rest	GADD45A [#] , EFNA1	98.8	96.0	90.6
NPS vs. Rest	EFNA1, MIR646HG	98.5	97.0	91.7
NPS vs. Rest	MIR646HG, KLF14	98.4	93.4	89.8
NPS vs. Rest	MLLT1, MIR646HG	98.3	97.5	86.6
NPS vs. Rest	ARG1*, MLLT1	97.7	90.9	88.3
NPS vs. Rest	MLLT1, EFNA1	97.7	91.4	88.7
NPS vs. Rest	MLLT1, NSUN7	97.7	92.4	81.2
NPS vs. Rest	EFNA1, NSUN7	97.5	85.1	92.4
NPS vs. Rest	SLC51A, EFNA1	97.4	89.8	90.5
NPS vs. Rest	EFNA1, KLF14	97.4	88.0	92.7
NPS vs. Rest	ZDHHC19, EFNA1	97.3	86.1	89.0
NPS vs. Rest	EFNA1, AGFG1	97.3	87.5	90.3
NPS vs. Rest	NSUN7, KLF14	97.3	95.4	91.8
NPS vs. Rest	EFNA1, PFKFB2 [#]	97.2	88.7	87.9
NPS vs. Rest	MLLT1, KLF14	97.2	92.3	86.4
INF vs. Rest	FECH*, TFEC	91.3	83.0	83.0
INF vs. Rest	TFEC, IFIT1B	90.3	80.9	80.9
INF vs. Rest	FECH*, RNF182	90.0	84.1	81.0
INF vs. Rest	IFIT1B, FECH*	89.9	81.6	79.2
INF vs. Rest	FECH*, APOL4	89.4	82.5	79.5
INF vs. Rest	FECH*, GYPA	89.4	81.7	80.4
INF vs. Rest	ITLN1, FECH*	89.4	82.3	81.3
INF vs. Rest	FECH*, THEM5	89.4	82.5	80.9
INF vs. Rest	IFIT1B, CA1*	89.4	82.2	80.9
INF vs. Rest	RHAG, FECH*	89.3	81.4	80.5
INF vs. Rest	FECH*, FAM83A	89.3	80.6	80.2
INF vs. Rest	RHCE, FECH*	89.3	79.1	80.4
INF vs. Rest	TFEC, CA1*	89.3	89.0	78.9
INF vs. Rest	SPTA1, FECH*	89.1	81.1	80.7
IHD vs. Rest	MAP7, SPRED1	94.4	87.3	85.3
IHD vs. Rest	SPRED1, GPR34	93.5	88.3	83.4
IHD vs. Rest	IL5RA, SPRED1	92.6	82.0	81.5
IHD vs. Rest	SPRED1, TPRG1	91.7	87.3	78.4
IHD vs. Rest	HRK, SPRED1	91.6	80.3	81.2
IHD vs. Rest	SPRED1, PLCB1	91.2	90.0	82.5
IHD vs. Rest	TRIM2, SPRED1	90.7	82.3	80.7
IHD vs. Rest	SIGLEC8, SPRED1	90.6	76.4	80.6

IHD vs. Rest	SMPD3, SPRED1	90.5	78.7	78.8
IHD vs. Rest	SPRED1, ZNF600	90.5	81.2	81.2
IHD vs. Rest	SPRED1, SDC2	90.3	79.9	82.2
IHD vs. Rest	MAP7, GPR34	89.9	86.8	80.2
IHD vs. Rest	PRSS33, SPRED1	89.8	78.2	79
IHD vs. Rest	SPRED1, DYNC2H1	89.6	82.4	79.8
IHD vs. Rest	CACNA2D3, SPRED1	89.1	78.0	78.6
IFN vs. Rest	ETV7, PLEKHO1*	92.5	89.6	78.1
IFN vs. Rest	IFITM3, ETV7	91.9	83.9	79.7
IFN vs. Rest	ETV7, APOL1*	91.7	89.4	79.9
IFN vs. Rest	BATF2, ETV7	91.7	88.8	78.1
IFN vs. Rest	PLEKHO1*, BATF2	91.7	89	78.6
IFN vs. Rest	ETV7, EPSTI1*	91.4	83.2	76.2
IFN vs. Rest	USP18, EPSTI1*	91.1	88.1	74.2
IFN vs. Rest	EPSTI1*, BATF2	91.0	83.2	75.6
IFN vs. Rest	IFITM3, BATF2	90.8	83.6	78.2
IFN vs. Rest	ETV7, SEPTIN4	90.2	86.7	78.3
IFN vs. Rest	ETV7, LAMP3	90.1	83.6	76.5
IFN vs. Rest	SERPING1, BATF2	90	87.4	76.3
IFN vs. Rest	LAMP3, BATF2	89.5	83.6	77
IFN vs. Rest	LAMP3, SERPING1	87.5	81.3	76.8
ADA vs. Rest	LGALS3BP, OTOF	88.2	77.5	85.9
ADA vs. Rest	LGALS3BP, IFI27	87.6	78.3	82.2
ADA vs. Rest	LGALS3BP, KIF14	87.5	76.7	81.4
ADA vs. Rest	LGALS3BP, CENPF	87.1	78.7	83.2
ADA vs. Rest	GTSE1, LGALS3BP	86.9	75.9	83.6
ADA vs. Rest	LGALS3BP, KCTD14	86.9	75.1	83.3
ADA vs. Rest	LGALS3BP, PDIA4	86.9	76.1	83.9
ADA vs. Rest	LGALS3BP, TSHR	86.7	75.6	82.1
ADA vs. Rest	LGALS3BP, PLAAT2	86.6	75.3	80.6
ADA vs. Rest	OTOF, IFI27	86.6	75.8	86.0
ADA vs. Rest	IGF1, LGALS3BP	86.2	75.6	82.1
ADA vs. Rest	CDC45, LGALS3BP	86.2	75.2	83.0
ADA vs. Rest	LGALS3BP, KIF15	86.2	75.6	83.2
ADA vs. Rest	IGLL5, LGALS3BP	86.2	76.7	80.4
ADA vs. Rest	LGALS3BP, MIXL1	86.1	74.1	82.7

Genes with * in column 2 include instances where one member of the pair was reported in previous endotype papers, although never partnered with the other gene in the pair. Genes with # are where ambiguous relationships with endotypes were reported.

Table 6: Expanded list of Gene Pairs that classify into specific endotypes when compared to all others.

Compare	Gene Pair	ROC	Sens	Spec	Compare	Gene Pair	ROC	Sens	Spec
NPS vs Rest	ATP9A/EPB41L4B	90	86	78	INF vs Rest	TSPO2/RHCE	84	66	77
NPS vs Rest	ATP9A/IL1R1	95	93	83	INF vs Rest	TSPO2/THEM5	85	74	77
NPS vs Rest	ATP9A/GADD45A	95	96	84	INF vs Rest	TSPO2/IFIT1B	88	73	79
NPS vs Rest	ATP9A/ARG1	97	95	86	INF vs Rest	TSPO2/CARD17	81	69	73
NPS vs Rest	ATP9A/PFKFB2	92	94	80	INF vs Rest	CD274/TMCC2	83	69	74
NPS vs Rest	ATP9A/MLLT1	95	91	80	INF vs Rest	CD274/CA1	88	88	76
NPS vs Rest	ATP9A/ANXA3	92	90	77	INF vs Rest	CD274/DYRK3	80	68	74
NPS vs Rest	ATP9A/GPR84	91	85	80	INF vs Rest	CD274/FAM83A	83	71	77
NPS vs Rest	ATP9A/OLAH	95	89	82	INF vs Rest	CD274/TLCD4	84	73	74
NPS vs Rest	ATP9A/ADAMTS3	92	87	83	INF vs Rest	CD274/KLHDC8A	77	72	67
NPS vs Rest	ATP9A/PCOLCE2	92	87	83	INF vs Rest	CD274/SPTA1	83	70	76
NPS vs Rest	ATP9A/ZDHHC19	94	90	82	INF vs Rest	CD274/TSPAN5	86	80	81
NPS vs Rest	ATP9A/SLC51A	93	90	82	INF vs Rest	CD274/GYP A	85	77	76
NPS vs Rest	ATP9A/HPGD	94	96	82	INF vs Rest	CD274/ITLN1	81	73	74
NPS vs Rest	ATP9A/SEMA6B	90	87	78	INF vs Rest	CD274/RNF182	84	77	79
NPS vs Rest	ATP9A/EFNA1	97	88	89	INF vs Rest	CD274/GLRX5	86	80	76
NPS vs Rest	ATP9A/AGFG1	94	92	81	INF vs Rest	CD274/RHCE	85	72	78
NPS vs Rest	ATP9A/NSUN7	96	97	82	INF vs Rest	CD274/THEM5	83	72	78
NPS vs Rest	ATP9A/TNFAIP8L3	91	87	80	INF vs Rest	CD274/IFIT1B	88	80	79
NPS vs Rest	ATP9A/KREMEN1	90	90	76	INF vs Rest	TMCC2/CA1	87	81	77
NPS vs Rest	ATP9A/ORM2	91	94	79	INF vs Rest	TMCC2/DYRK3	84	66	77
NPS vs Rest	ATP9A/MIR646HG	95	92	83	INF vs Rest	TMCC2/FAM83A	86	73	77
NPS vs Rest	ATP9A/KLF14	96	94	87	INF vs Rest	TMCC2/TLCD4	86	76	76
NPS vs Rest	EPB41L4B/IL1R1	89	76	81	INF vs Rest	TMCC2/ANKRD22	83	68	74
NPS vs Rest	EPB41L4B/GADD45A	93	87	82	INF vs Rest	TMCC2/GBP5	82	70	74
NPS vs Rest	EPB41L4B/ARG1	92	92	82	INF vs Rest	TMCC2/KLHDC8A	83	70	76
NPS vs Rest	EPB41L4B/PFKFB2	88	82	75	INF vs Rest	TMCC2/SPTA1	85	74	76
NPS vs Rest	EPB41L4B/MLLT1	94	86	83	INF vs Rest	TMCC2/TSPAN5	87	74	80
NPS vs Rest	EPB41L4B/ANXA3	89	86	75	INF vs Rest	TMCC2/GYP A	87	75	76
NPS vs Rest	EPB41L4B/GPR84	85	77	81	INF vs Rest	TMCC2/P2RY14	82	68	74
NPS vs Rest	EPB41L4B/OLAH	87	69	80	INF vs Rest	TMCC2/ITLN1	85	72	80
NPS vs Rest	EPB41L4B/ADAMTS3	87	79	86	INF vs Rest	TMCC2/RNF182	86	79	78
NPS vs Rest	EPB41L4B/PCOLCE2	80	71	83	INF vs Rest	TMCC2/GLRX5	86	75	77
NPS vs Rest	EPB41L4B/ZDHHC19	89	78	82	INF vs Rest	TMCC2/RHCE	85	73	78
NPS vs Rest	EPB41L4B/SLC51A	92	85	83	INF vs Rest	TMCC2/THEM5	86	74	79
NPS vs Rest	EPB41L4B/HPGD	88	71	79	INF vs Rest	TMCC2/IFIT1B	88	77	81
NPS vs Rest	EPB41L4B/SEMA6B	84	77	75	INF vs Rest	TMCC2/CARD17	82	69	74
NPS vs Rest	EPB41L4B/EFNA1	95	83	90	INF vs Rest	CA1/DYRK3	87	83	76
NPS vs Rest	EPB41L4B/AGFG1	92	87	80	INF vs Rest	CA1/FAM83A	88	85	77
NPS vs Rest	EPB41L4B/NSUN7	94	95	82	INF vs Rest	CA1/TLCD4	88	84	78
NPS vs Rest	EPB41L4B/TNFAIP8L3	85	79	81	INF vs Rest	CA1/ANKRD22	87	88	75
NPS vs Rest	EPB41L4B/KREMEN1	81	77	72	INF vs Rest	CA1/GBP5	87	88	76
NPS vs Rest	EPB41L4B/MIR646HG	90	84	80	INF vs Rest	CA1/KLHDC8A	87	84	76
NPS vs Rest	EPB41L4B/KLF14	93	89	87	INF vs Rest	CA1/SPTA1	88	83	78
NPS vs Rest	IL1R1/GADD45A	96	89	85	INF vs Rest	CA1/TSPAN5	89	85	80

NPS vs Rest	IL1R1/ARG1	93	82	84	INF vs Rest	CA1/GYP A	88	82	76
NPS vs Rest	IL1R1/PFKFB2	92	80	81	INF vs Rest	CA1/P2RY14	87	88	76
NPS vs Rest	IL1R1/MLLT1	96	90	86	INF vs Rest	CA1/ITLN1	87	82	77
NPS vs Rest	IL1R1/ANXA3	93	87	83	INF vs Rest	CA1/RNF182	89	82	78
NPS vs Rest	IL1R1/GPR84	95	87	87	INF vs Rest	CA1/GLRX5	88	85	78
NPS vs Rest	IL1R1/OLAH	92	73	86	INF vs Rest	CA1/RHCE	88	82	78
NPS vs Rest	IL1R1/ADAMTS3	92	81	85	INF vs Rest	CA1/THEM5	88	83	80
NPS vs Rest	IL1R1/PCOLCE2	92	79	85	INF vs Rest	CA1/IFIT1B	89	82	81
NPS vs Rest	IL1R1/ZDHHC19	95	83	86	INF vs Rest	CA1/CARD17	87	88	74
NPS vs Rest	IL1R1/SLC51A	95	86	86	INF vs Rest	DYRK3/FAM83A	85	70	76
NPS vs Rest	IL1R1/HPGD	92	79	86	INF vs Rest	DYRK3/TLCD4	84	71	77
NPS vs Rest	IL1R1/SEMA6B	94	89	84	INF vs Rest	DYRK3/ANKRD22	80	68	75
NPS vs Rest	IL1R1/EFNA1	96	78	92	INF vs Rest	DYRK3/GBP5	79	68	73
NPS vs Rest	IL1R1/AGFG1	94	90	85	INF vs Rest	DYRK3/KLHDC8A	81	65	74
NPS vs Rest	IL1R1/NSUN7	95	90	84	INF vs Rest	DYRK3/SPTA1	84	72	79
NPS vs Rest	IL1R1/TNFAIP8L3	95	93	85	INF vs Rest	DYRK3/TSPAN5	86	74	80
NPS vs Rest	IL1R1/KREMEN1	91	87	82	INF vs Rest	DYRK3/GYP A	86	74	76
NPS vs Rest	IL1R1/ORM2	91	85	83	INF vs Rest	DYRK3/P2RY14	79	67	74
NPS vs Rest	IL1R1/MIR646HG	95	92	85	INF vs Rest	DYRK3/ITLN1	84	70	79
NPS vs Rest	IL1R1/KLF14	96	87	90	INF vs Rest	DYRK3/RNF182	85	76	79
NPS vs Rest	GADD45A/ARG1	96	95	83	INF vs Rest	DYRK3/GLRX5	86	75	76
NPS vs Rest	GADD45A/PFKFB2	94	93	80	INF vs Rest	DYRK3/RHCE	85	69	78
NPS vs Rest	GADD45A/MLLT1	97	94	86	INF vs Rest	DYRK3/THEM5	85	77	79
NPS vs Rest	GADD45A/ANXA3	95	90	84	INF vs Rest	DYRK3/IFIT1B	88	75	80
NPS vs Rest	GADD45A/GPR84	94	88	84	INF vs Rest	DYRK3/CARD17	80	66	74
NPS vs Rest	GADD45A/OLAH	95	90	85	INF vs Rest	FAM83A/TLCD4	88	78	78
NPS vs Rest	GADD45A/ADAMTS3	95	93	86	INF vs Rest	FAM83A/ANKRD22	83	70	77
NPS vs Rest	GADD45A/PCOLCE2	93	85	84	INF vs Rest	FAM83A/GBP5	82	70	77
NPS vs Rest	GADD45A/ZDHHC19	95	89	87	INF vs Rest	FAM83A/KLHDC8A	84	70	76
NPS vs Rest	GADD45A/SLC51A	95	92	87	INF vs Rest	FAM83A/SPTA1	87	75	78
NPS vs Rest	GADD45A/HPGD	95	88	85	INF vs Rest	FAM83A/TSPAN5	88	79	81
NPS vs Rest	GADD45A/SEMA6B	93	87	83	INF vs Rest	FAM83A/GYP A	87	77	78
NPS vs Rest	GADD45A/EFNA1	99	96	91	INF vs Rest	FAM83A/P2RY14	83	69	77
NPS vs Rest	GADD45A/AGFG1	95	88	83	INF vs Rest	FAM83A/ITLN1	85	80	83
NPS vs Rest	GADD45A/NSUN7	97	99	86	INF vs Rest	FAM83A/RNF182	88	80	78
NPS vs Rest	GADD45A/TNFAIP8L3	94	86	85	INF vs Rest	FAM83A/GLRX5	87	79	76
NPS vs Rest	GADD45A/KREMEN1	94	93	84	INF vs Rest	FAM83A/RHCE	86	75	78
NPS vs Rest	GADD45A/ORM2	96	94	84	INF vs Rest	FAM83A/THEM5	86	75	80
NPS vs Rest	GADD45A/MIR646HG	97	97	85	INF vs Rest	FAM83A/IFIT1B	89	79	82
NPS vs Rest	GADD45A/KLF14	95	93	90	INF vs Rest	FAM83A/CARD17	83	71	77
NPS vs Rest	ARG1/PFKFB2	94	94	80	INF vs Rest	TLCD4/ANKRD22	84	71	74
NPS vs Rest	ARG1/MLLT1	98	91	88	INF vs Rest	TLCD4/GBP5	84	73	74
NPS vs Rest	ARG1/ANXA3	94	86	83	INF vs Rest	TLCD4/KLHDC8A	84	78	73
NPS vs Rest	ARG1/GPR84	96	89	87	INF vs Rest	TLCD4/SPTA1	85	74	78
NPS vs Rest	ARG1/OLAH	94	86	83	INF vs Rest	TLCD4/TSPAN5	87	73	79
NPS vs Rest	ARG1/ADAMTS3	95	90	87	INF vs Rest	TLCD4/GYP A	87	74	76
NPS vs Rest	ARG1/PCOLCE2	93	86	84	INF vs Rest	TLCD4/P2RY14	84	72	75
NPS vs Rest	ARG1/ZDHHC19	95	98	87	INF vs Rest	TLCD4/ITLN1	86	75	77
NPS vs Rest	ARG1/SLC51A	96	91	86	INF vs Rest	TLCD4/RNF182	87	79	79
NPS vs Rest	ARG1/HPGD	94	81	86	INF vs Rest	TLCD4/GLRX5	87	76	76

NPS vs Rest	ARG1/SEMA6B	96	91	87	INF vs Rest	TLCD4/RHCE	86	74	78
NPS vs Rest	ARG1/EFNA1	97	80	92	INF vs Rest	TLCD4/THEM5	88	80	80
NPS vs Rest	ARG1/AGFG1	96	88	86	INF vs Rest	TLCD4/IFIT1B	89	79	79
NPS vs Rest	ARG1/NSUN7	96	95	86	INF vs Rest	TLCD4/CARD17	84	72	74
NPS vs Rest	ARG1/TNFAIP8L3	95	86	87	INF vs Rest	ANKRD22/KLHDC8A	77	67	68
NPS vs Rest	ARG1/KREMEN1	95	89	85	INF vs Rest	ANKRD22/SPTA1	83	69	74
NPS vs Rest	ARG1/ORM2	93	81	84	INF vs Rest	ANKRD22/TSPAN5	86	75	78
NPS vs Rest	ARG1/MIR646HG	97	98	87	INF vs Rest	ANKRD22/GYP A	85	75	76
NPS vs Rest	ARG1/KLF14	96	95	89	INF vs Rest	ANKRD22/ITLN1	81	75	74
NPS vs Rest	PFKFB2/MLLT1	95	95	83	INF vs Rest	ANKRD22/RNF182	83	78	78
NPS vs Rest	PFKFB2/ANXA3	92	90	77	INF vs Rest	ANKRD22/GLRX5	86	80	75
NPS vs Rest	PFKFB2/GPR84	92	87	79	INF vs Rest	ANKRD22/RHCE	84	74	78
NPS vs Rest	PFKFB2/OLAH	92	84	81	INF vs Rest	ANKRD22/THEM5	83	71	77
NPS vs Rest	PFKFB2/ADAMTS3	91	86	81	INF vs Rest	ANKRD22/IFIT1B	88	78	81
NPS vs Rest	PFKFB2/PCOLCE2	90	84	79	INF vs Rest	GBP5/KLHDC8A	77	71	68
NPS vs Rest	PFKFB2/ZDHHC19	94	89	83	INF vs Rest	GBP5/SPTA1	82	70	76
NPS vs Rest	PFKFB2/SLC51A	93	87	83	INF vs Rest	GBP5/TSPAN5	86	78	79
NPS vs Rest	PFKFB2/HPGD	91	87	80	INF vs Rest	GBP5/GYP A	85	79	75
NPS vs Rest	PFKFB2/SEMA6B	89	81	78	INF vs Rest	GBP5/ITLN1	81	74	74
NPS vs Rest	PFKFB2/EFNA1	97	89	88	INF vs Rest	GBP5/RNF182	84	74	77
NPS vs Rest	PFKFB2/AGFG1	92	92	80	INF vs Rest	GBP5/GLRX5	86	80	75
NPS vs Rest	PFKFB2/NSUN7	95	97	81	INF vs Rest	GBP5/RHCE	84	73	77
NPS vs Rest	PFKFB2/TNFAIP8L3	91	86	80	INF vs Rest	GBP5/THEM5	82	71	77
NPS vs Rest	PFKFB2/KREMEN1	90	90	78	INF vs Rest	GBP5/IFIT1B	88	79	77
NPS vs Rest	PFKFB2/ORM2	90	88	78	INF vs Rest	KLHDC8A/SPTA1	82	75	73
NPS vs Rest	PFKFB2/MIR646HG	93	89	80	INF vs Rest	KLHDC8A/TSPAN5	86	79	77
NPS vs Rest	PFKFB2/KLF14	95	94	87	INF vs Rest	KLHDC8A/GYP A	86	75	74
NPS vs Rest	MLLT1/ANXA3	94	84	82	INF vs Rest	KLHDC8A/P2RY14	77	70	68
NPS vs Rest	MLLT1/GPR84	94	82	83	INF vs Rest	KLHDC8A/ITLN1	82	72	76
NPS vs Rest	MLLT1/OLAH	96	91	85	INF vs Rest	KLHDC8A/RNF182	85	80	77
NPS vs Rest	MLLT1/ADAMTS3	95	90	85	INF vs Rest	KLHDC8A/GLRX5	86	78	75
NPS vs Rest	MLLT1/PCOLCE2	93	78	85	INF vs Rest	KLHDC8A/RHCE	84	74	76
NPS vs Rest	MLLT1/ZDHHC19	94	82	83	INF vs Rest	KLHDC8A/THEM5	84	73	77
NPS vs Rest	MLLT1/SLC51A	95	81	84	INF vs Rest	KLHDC8A/IFIT1B	88	77	80
NPS vs Rest	MLLT1/HPGD	96	85	86	INF vs Rest	KLHDC8A/CARD17	76	71	67
NPS vs Rest	MLLT1/SEMA6B	93	84	82	INF vs Rest	SPTA1/TSPAN5	87	79	80
NPS vs Rest	MLLT1/EFNA1	98	91	89	INF vs Rest	SPTA1/GYP A	86	72	78
NPS vs Rest	MLLT1/AGFG1	95	86	85	INF vs Rest	SPTA1/P2RY14	82	69	75
NPS vs Rest	MLLT1/NSUN7	98	92	81	INF vs Rest	SPTA1/ITLN1	85	77	79
NPS vs Rest	MLLT1/TNFAIP8L3	93	80	83	INF vs Rest	SPTA1/RNF182	86	77	79
NPS vs Rest	MLLT1/KREMEN1	94	88	83	INF vs Rest	SPTA1/GLRX5	86	78	78
NPS vs Rest	MLLT1/ORM2	94	87	83	INF vs Rest	SPTA1/RHCE	86	72	77
NPS vs Rest	MLLT1/MIR646HG	98	98	87	INF vs Rest	SPTA1/THEM5	87	74	81
NPS vs Rest	MLLT1/KLF14	97	92	86	INF vs Rest	SPTA1/IFIT1B	88	81	82
NPS vs Rest	ANXA3/GPR84	89	79	79	INF vs Rest	SPTA1/CARD17	82	72	75
NPS vs Rest	ANXA3/OLAH	93	88	83	INF vs Rest	TSPAN5/GYP A	88	74	80
NPS vs Rest	ANXA3/ADAMTS3	92	84	83	INF vs Rest	TSPAN5/P2RY14	86	76	79
NPS vs Rest	ANXA3/PCOLCE2	90	79	81	INF vs Rest	TSPAN5/ITLN1	87	76	81
NPS vs Rest	ANXA3/ZDHHC19	92	82	83	INF vs Rest	TSPAN5/RNF182	89	79	79
NPS vs Rest	ANXA3/SLC51A	92	81	82	INF vs Rest	TSPAN5/GLRX5	87	80	79

NPS vs Rest	ANXA3/HPGD	94	78	83	INF vs Rest	TSPAN5/RHCE	88	74	82
NPS vs Rest	ANXA3/SEMA6B	88	81	78	INF vs Rest	TSPAN5/THEM5	88	80	79
NPS vs Rest	ANXA3/EFNA1	96	83	89	INF vs Rest	TSPAN5/IFIT1B	89	77	81
NPS vs Rest	ANXA3/AGFG1	93	82	83	INF vs Rest	TSPAN5/CARD17	86	78	78
NPS vs Rest	ANXA3/NSUN7	96	94	83	INF vs Rest	GYPAP2RY14	85	76	74
NPS vs Rest	ANXA3/TNFAIP8L3	90	83	79	INF vs Rest	GYPATLNL1	86	77	76
NPS vs Rest	ANXA3/KREMEN1	89	80	75	INF vs Rest	GYPARNF182	88	80	80
NPS vs Rest	ANXA3/ORM2	88	77	76	INF vs Rest	GYPAGLRX5	87	75	75
NPS vs Rest	ANXA3/MIR646HG	95	94	81	INF vs Rest	GYPARHCE	87	74	78
NPS vs Rest	ANXA3/KLF14	95	94	86	INF vs Rest	GYPATHEM5	88	77	79
NPS vs Rest	GPR84/OLAH	93	84	86	INF vs Rest	GYPA/IFIT1B	89	79	81
NPS vs Rest	GPR84/ADAMTS3	90	76	84	INF vs Rest	GYPACARD17	85	78	75
NPS vs Rest	GPR84/PCOLCE2	87	77	83	INF vs Rest	P2RY14/ITLNL1	81	68	74
NPS vs Rest	GPR84/ZDHHC19	91	84	82	INF vs Rest	P2RY14/RNF182	83	74	78
NPS vs Rest	GPR84/SLC51A	91	75	82	INF vs Rest	P2RY14/GLRX5	86	80	76
NPS vs Rest	GPR84/HPGD	93	86	83	INF vs Rest	P2RY14/RHCE	84	70	77
NPS vs Rest	GPR84/SEMA6B	85	80	79	INF vs Rest	P2RY14/THEM5	82	70	77
NPS vs Rest	GPR84/EFNA1	97	88	90	INF vs Rest	P2RY14/IFIT1B	88	78	79
NPS vs Rest	GPR84/AGFG1	93	83	83	INF vs Rest	ITLNL1/RNF182	87	81	81
NPS vs Rest	GPR84/NSUN7	97	99	84	INF vs Rest	ITLNL1/GLRX5	87	75	76
NPS vs Rest	GPR84/TNFAIP8L3	87	76	81	INF vs Rest	ITLNL1/RHCE	86	74	79
NPS vs Rest	GPR84/KREMEN1	86	78	76	INF vs Rest	ITLNL1/THEM5	84	76	79
NPS vs Rest	GPR84/ORM2	86	78	79	INF vs Rest	ITLNL1/IFIT1B	88	78	81
NPS vs Rest	GPR84/MIR646HG	95	90	83	INF vs Rest	ITLNL1/CARD17	81	74	75
NPS vs Rest	GPR84/KLF14	93	90	88	INF vs Rest	RNF182/GLRX5	89	75	79
NPS vs Rest	OLAH/ADAMTS3	92	78	84	INF vs Rest	RNF182/RHCE	88	80	81
NPS vs Rest	OLAH/PCOLCE2	90	74	86	INF vs Rest	RNF182/THEM5	87	78	82
NPS vs Rest	OLAH/ZDHHC19	94	77	85	INF vs Rest	RNF182/IFIT1B	89	84	81
NPS vs Rest	OLAH/SLC51A	95	86	86	INF vs Rest	RNF182/CARD17	84	77	79
NPS vs Rest	OLAH/HPGD	92	75	84	INF vs Rest	GLRX5/RHCE	87	76	78
NPS vs Rest	OLAH/SEMA6B	93	89	82	INF vs Rest	GLRX5/THEM5	87	79	77
NPS vs Rest	OLAH/EFNA1	96	83	90	INF vs Rest	GLRX5/IFIT1B	88	79	80
NPS vs Rest	OLAH/AGFG1	94	88	84	INF vs Rest	GLRX5/CARD17	86	80	75
NPS vs Rest	OLAH/NSUN7	95	91	85	INF vs Rest	RHCE/THEM5	87	75	80
NPS vs Rest	OLAH/TNFAIP8L3	93	84	86	INF vs Rest	RHCE/IFIT1B	89	75	81
NPS vs Rest	OLAH/KREMEN1	91	80	84	INF vs Rest	RHCE/CARD17	84	72	79
NPS vs Rest	OLAH/ORM2	89	75	83	INF vs Rest	THEM5/IFIT1B	89	78	82
NPS vs Rest	OLAH/MIR646HG	96	94	89	INF vs Rest	THEM5/CARD17	82	72	78
NPS vs Rest	OLAH/KLF14	95	94	90	INF vs Rest	IFIT1B/CARD17	88	78	76
NPS vs Rest	ADAMTS3/PCOLCE2	87	77	84	IHD Endotype				
NPS vs Rest	ADAMTS3/ZDHHC19	92	85	85	IHD vs Rest	IL5RA/TRIM2	78	61	74
NPS vs Rest	ADAMTS3/SLC51A	93	86	86	IHD vs Rest	IL5RA/SPRED1	93	82	82
NPS vs Rest	ADAMTS3/HPGD	92	78	84	IHD vs Rest	IL5RA/GPR34	82	73	73
NPS vs Rest	ADAMTS3/SEMA6B	89	79	83	IHD vs Rest	IL5RA/PLCB1	80	71	73
NPS vs Rest	ADAMTS3/EFNA1	96	82	91	IHD vs Rest	IL5RA/DYNC2H1	76	62	72
NPS vs Rest	ADAMTS3/AGFG1	93	87	86	IHD vs Rest	SMPD3/TRIM2	76	62	71
NPS vs Rest	ADAMTS3/NSUN7	95	93	86	IHD vs Rest	SMPD3/MAP7	75	69	71
NPS vs Rest	ADAMTS3/TNFAIP8L3	90	77	85	IHD vs Rest	SMPD3/SPRED1	91	79	79
NPS vs Rest	ADAMTS3/KREMEN1	88	82	80	IHD vs Rest	SMPD3/GPR34	81	71	75
NPS vs Rest	ADAMTS3/ORM2	89	78	81	IHD vs Rest	SMPD3/PLCB1	80	72	72

NPS vs Rest	ADAMTS3/MIR646HG	93	84	85	IHD vs Rest	SMPD3/DYNC2H1	76	62	70
NPS vs Rest	ADAMTS3/KLF14	94	89	88	IHD vs Rest	PRSS33/SPRED1	90	78	79
NPS vs Rest	PCOLCE2/ZDHHC19	90	78	85	IHD vs Rest	PRSS33/GPR34	80	74	74
NPS vs Rest	PCOLCE2/SLC51A	91	74	85	IHD vs Rest	PRSS33/PLCB1	79	67	71
NPS vs Rest	PCOLCE2/HPGD	89	74	83	IHD vs Rest	SIGLEC8/TRIM2	77	63	73
NPS vs Rest	PCOLCE2/SEMA6B	85	77	81	IHD vs Rest	SIGLEC8/MAP7	76	69	73
NPS vs Rest	PCOLCE2/EFNA1	96	79	92	IHD vs Rest	SIGLEC8/SPRED1	91	76	81
NPS vs Rest	PCOLCE2/AGFG1	92	82	84	IHD vs Rest	SIGLEC8/GPR34	81	74	75
NPS vs Rest	PCOLCE2/NSUN7	96	92	84	IHD vs Rest	SIGLEC8/PLCB1	80	68	72
NPS vs Rest	PCOLCE2/TNFAIP8L3	85	75	83	IHD vs Rest	SIGLEC8/DYNC2H1	76	66	72
NPS vs Rest	PCOLCE2/KREMEN1	89	77	81	IHD vs Rest	TRIM2/HRK	76	64	70
NPS vs Rest	PCOLCE2/ORM2	86	71	80	IHD vs Rest	TRIM2/MAP7	88	80	79
NPS vs Rest	PCOLCE2/MIR646HG	95	86	87	IHD vs Rest	TRIM2/CACNA2D3	79	70	71
NPS vs Rest	PCOLCE2/KLF14	92	88	88	IHD vs Rest	TRIM2/SPRED1	91	82	81
NPS vs Rest	ZDHHC19/SLC51A	92	76	83	IHD vs Rest	TRIM2/SDC2	79	68	73
NPS vs Rest	ZDHHC19/HPGD	93	84	85	IHD vs Rest	TRIM2/GPR82	78	66	71
NPS vs Rest	ZDHHC19/SEMA6B	90	84	82	IHD vs Rest	TRIM2/GPR34	85	78	75
NPS vs Rest	ZDHHC19/EFNA1	97	86	89	IHD vs Rest	TRIM2/GRAMD1C	76	66	70
NPS vs Rest	ZDHHC19/AGFG1	95	89	85	IHD vs Rest	TRIM2/PLCB1	84	81	76
NPS vs Rest	ZDHHC19/NSUN7	96	100	87	IHD vs Rest	TRIM2/DYNC2H1	80	63	73
NPS vs Rest	ZDHHC19/TNFAIP8L3	91	82	84	IHD vs Rest	TRIM2/TPRG1	79	71	71
NPS vs Rest	ZDHHC19/KREMEN1	91	82	83	IHD vs Rest	TRIM2/ZNF600	80	68	72
NPS vs Rest	ZDHHC19/ORM2	91	86	81	IHD vs Rest	ADAM23/MAP7	79	72	72
NPS vs Rest	ZDHHC19/MIR646HG	96	94	83	IHD vs Rest	ADAM23/SPRED1	89	86	76
NPS vs Rest	ZDHHC19/KLF14	95	89	88	IHD vs Rest	ADAM23/GPR34	80	77	73
NPS vs Rest	SLC51A/HPGD	95	87	88	IHD vs Rest	ADAM23/PLCB1	77	74	70
NPS vs Rest	SLC51A/SEMA6B	91	74	82	IHD vs Rest	HRK/MAP7	77	64	75
NPS vs Rest	SLC51A/EFNA1	97	90	91	IHD vs Rest	HRK/SPRED1	92	80	81
NPS vs Rest	SLC51A/AGFG1	95	83	85	IHD vs Rest	HRK/GPR34	83	73	75
NPS vs Rest	SLC51A/NSUN7	96	94	87	IHD vs Rest	HRK/PLCB1	79	69	72
NPS vs Rest	SLC51A/TNFAIP8L3	91	75	84	IHD vs Rest	HRK/DYNC2H1	75	64	72
NPS vs Rest	SLC51A/KREMEN1	92	80	82	IHD vs Rest	HRK/ZNF600	77	64	70
NPS vs Rest	SLC51A/ORM2	93	77	82	IHD vs Rest	MAP7/CACNA2D3	76	64	71
NPS vs Rest	SLC51A/MIR646HG	96	94	84	IHD vs Rest	MAP7/BAALC	77	70	67
NPS vs Rest	SLC51A/KLF14	96	90	90	IHD vs Rest	MAP7/SPRED1	94	87	85
NPS vs Rest	HPGD/SEMA6B	91	75	83	IHD vs Rest	MAP7/GPR82	85	68	78
NPS vs Rest	HPGD/EFNA1	97	76	91	IHD vs Rest	MAP7/GPR34	90	87	80
NPS vs Rest	HPGD/AGFG1	94	86	84	IHD vs Rest	MAP7/GRAMD1C	75	65	74
NPS vs Rest	HPGD/NSUN7	96	86	85	IHD vs Rest	MAP7/PLCB1	86	76	77
NPS vs Rest	HPGD/TNFAIP8L3	93	82	84	IHD vs Rest	MAP7/DYNC2H1	84	72	79
NPS vs Rest	HPGD/KREMEN1	92	82	82	IHD vs Rest	MAP7/TPRG1	80	71	73
NPS vs Rest	HPGD/ORM2	93	89	86	IHD vs Rest	MAP7/ZNF600	86	74	76
NPS vs Rest	HPGD/MIR646HG	97	95	88	IHD vs Rest	CACNA2D3/SPRED1	89	78	79
NPS vs Rest	HPGD/KLF14	95	95	89	IHD vs Rest	CACNA2D3/GPR34	82	73	74
NPS vs Rest	SEMA6B/EFNA1	95	80	88	IHD vs Rest	CACNA2D3/PLCB1	80	75	71
NPS vs Rest	SEMA6B/AGFG1	91	83	81	IHD vs Rest	CACNA2D3/DYNC2H1	75	64	71
NPS vs Rest	SEMA6B/NSUN7	96	95	81	IHD vs Rest	CACNA2D3/ZNF600	77	80	68
NPS vs Rest	SEMA6B/TNFAIP8L3	86	76	79	IHD vs Rest	ALOX15/SPRED1	89	75	79
NPS vs Rest	SEMA6B/KREMEN1	85	78	73	IHD vs Rest	ALOX15/GPR34	81	72	74
NPS vs Rest	SEMA6B/ORM2	84	79	77	IHD vs Rest	ALOX15/PLCB1	78	67	73

NPS vs Rest	SEMA6B/MIR646HG	92	82	80	IHD vs Rest	BAALC/SPRED1	89	84	79
NPS vs Rest	SEMA6B/KLF14	93	81	86	IHD vs Rest	BAALC/GPR34	81	83	73
NPS vs Rest	EFNA1/AGFG1	97	88	90	IHD vs Rest	BAALC/PLCB1	78	79	68
NPS vs Rest	EFNA1/NSUN7	98	85	92	IHD vs Rest	SPRED1/SDC2	90	80	82
NPS vs Rest	EFNA1/TNFAIP8L3	96	88	92	IHD vs Rest	SPRED1/GPR82	89	76	79
NPS vs Rest	EFNA1/KREMEN1	95	85	90	IHD vs Rest	SPRED1/GPR34	94	88	83
NPS vs Rest	EFNA1/ORM2	94	83	90	IHD vs Rest	SPRED1/GRAMD1C	89	83	80
NPS vs Rest	EFNA1/MIR646HG	99	97	92	IHD vs Rest	SPRED1/PLCB1	91	90	83
NPS vs Rest	EFNA1/KLF14	97	88	93	IHD vs Rest	SPRED1/DYNC2H1	90	82	80
NPS vs Rest	AGFG1/NSUN7	96	95	82	IHD vs Rest	SPRED1/TPRG1	92	87	78
NPS vs Rest	AGFG1/TNFAIP8L3	93	85	84	IHD vs Rest	SPRED1/ZNF600	91	81	81
NPS vs Rest	AGFG1/KREMEN1	93	88	83	IHD vs Rest	SDC2/GPR34	84	69	79
NPS vs Rest	AGFG1/ORM2	93	82	82	IHD vs Rest	SDC2/PLCB1	81	75	73
NPS vs Rest	AGFG1/MIR646HG	95	93	87	IHD vs Rest	SDC2/DYNC2H1	77	58	74
NPS vs Rest	AGFG1/KLF14	97	95	89	IHD vs Rest	SDC2/ZNF600	81	77	76
NPS vs Rest	NSUN7/TNFAIP8L3	96	97	87	IHD vs Rest	GPR82/GPR34	80	71	76
NPS vs Rest	NSUN7/KREMEN1	95	91	80	IHD vs Rest	GPR82/GRAMD1C	76	68	69
NPS vs Rest	NSUN7/ORM2	95	93	82	IHD vs Rest	GPR82/PLCB1	84	79	73
NPS vs Rest	NSUN7/MIR646HG	96	97	84	IHD vs Rest	GPR82/DYNC2H1	77	69	73
NPS vs Rest	NSUN7/KLF14	97	95	92	IHD vs Rest	GPR82/TPRG1	77	65	68
NPS vs Rest	TNFAIP8L3/KREMEN1	89	80	79	IHD vs Rest	GPR82/ZNF600	78	69	70
NPS vs Rest	TNFAIP8L3/ORM2	88	76	82	IHD vs Rest	GPR34/GRAMD1C	81	75	74
NPS vs Rest	TNFAIP8L3/MIR646HG	94	85	84	IHD vs Rest	GPR34/PLCB1	88	87	78
NPS vs Rest	TNFAIP8L3/KLF14	93	84	87	IHD vs Rest	GPR34/DYNC2H1	83	70	81
NPS vs Rest	KREMEN1/ORM2	82	84	69	IHD vs Rest	GPR34/TPRG1	83	81	78
NPS vs Rest	KREMEN1/MIR646HG	93	85	79	IHD vs Rest	GPR34/ZNF600	84	80	79
NPS vs Rest	KREMEN1/KLF14	94	85	86	IHD vs Rest	GRAMD1C/PLCB1	77	70	70
NPS vs Rest	ORM2/MIR646HG	91	82	80	IHD vs Rest	GRAMD1C/DYNC2H1	75	63	71
NPS vs Rest	ORM2/KLF14	94	86	88	IHD vs Rest	GRAMD1C/ZNF600	76	75	69
NPS vs Rest	MIR646HG/KLF14	98	93	90	IHD vs Rest	PLCB1/DYNC2H1	83	76	77
INF Endotype					IHD vs Rest	PLCB1/TPRG1	82	83	70
INF vs Rest	FECH/APOL4	89	83	80	IHD vs Rest	PLCB1/ZNF600	83	78	73
INF vs Rest	FECH/RIOK3	89	79	79	IHD vs Rest	DYNC2H1/TPRG1	78	63	72
INF vs Rest	FECH/BNIP3L	89	83	81	IHD vs Rest	DYNC2H1/ZNF600	79	65	77
INF vs Rest	FECH/TFEC	91	83	83	IFN Endotype				
INF vs Rest	FECH/RHAG	89	81	81	IFN vs Rest	ETV7/PLEKHO1	93	90	78
INF vs Rest	FECH/TSP02	89	79	81	IFN vs Rest	ETV7/LAMP3	90	84	77
INF vs Rest	FECH/CD274	89	82	81	IFN vs Rest	ETV7/APOL1	92	89	80
INF vs Rest	FECH/TMCC2	89	79	79	IFN vs Rest	ETV7/SEPTIN4	90	87	78
INF vs Rest	FECH/CA1	90	83	79	IFN vs Rest	ETV7/EPSTI1	91	83	76
INF vs Rest	FECH/DYRK3	89	80	80	IFN vs Rest	ETV7/RSAD2	89	82	76
INF vs Rest	FECH/FAM83A	89	81	80	IFN vs Rest	ETV7/IFITM3	92	84	80
INF vs Rest	FECH/TLCD4	89	78	81	IFN vs Rest	ETV7/SERPING1	90	88	78
INF vs Rest	FECH/ANKRD22	89	82	79	IFN vs Rest	ETV7/CLEC4F	90	88	76
INF vs Rest	FECH/GBP5	89	83	79	IFN vs Rest	ETV7/TPPP3	90	87	77
INF vs Rest	FECH/KLHDC8A	89	83	78	IFN vs Rest	ETV7/LY6E	89	85	76
INF vs Rest	FECH/SPTA1	89	81	81	IFN vs Rest	ETV7/BATF2	92	89	78
INF vs Rest	FECH/TSPAN5	89	81	82	IFN vs Rest	ETV7/EXOC3L1	90	84	76
INF vs Rest	FECH/GYPA	89	82	80	IFN vs Rest	ETV7/HES4	89	84	76
INF vs Rest	FECH/P2RY14	89	82	80	IFN vs Rest	PLEKHO1/LAMP3	81	75	75

INF vs Rest	FECH/ITLN1	89	82	81	IFN vs Rest	PLEKHO1/APOL1	91	85	80
INF vs Rest	FECH/RNF182	90	84	81	IFN vs Rest	PLEKHO1/SEPTIN4	82	73	75
INF vs Rest	FECH/GLRX5	89	81	79	IFN vs Rest	PLEKHO1/EPSTI1	88	84	71
INF vs Rest	FECH/RHCE	89	79	80	IFN vs Rest	PLEKHO1/RSAD2	76	69	66
INF vs Rest	FECH/THEM5	89	83	81	IFN vs Rest	PLEKHO1/IFITM3	82	78	72
INF vs Rest	FECH/IFIT1B	90	82	79	IFN vs Rest	PLEKHO1/SERPING1	89	81	78
INF vs Rest	FECH/CARD17	88	82	79	IFN vs Rest	PLEKHO1/BATF2	92	89	79
INF vs Rest	APOL4/RIOK3	84	68	77	IFN vs Rest	PLEKHO1/EXOC3L1	78	70	71
INF vs Rest	APOL4/BNIP3L	86	75	77	IFN vs Rest	LAMP3/APOL1	89	85	80
INF vs Rest	APOL4/RHAG	83	70	72	IFN vs Rest	LAMP3/SEPTIN4	84	74	77
INF vs Rest	APOL4/TSP02	81	72	71	IFN vs Rest	LAMP3/EPSTI1	87	82	73
INF vs Rest	APOL4/TMCC2	83	75	73	IFN vs Rest	LAMP3/RSAD2	81	76	71
INF vs Rest	APOL4/CA1	88	87	75	IFN vs Rest	LAMP3/IFITM3	85	79	75
INF vs Rest	APOL4/DYRK3	81	73	73	IFN vs Rest	LAMP3/SERPING1	88	81	77
INF vs Rest	APOL4/FAM83A	82	68	77	IFN vs Rest	LAMP3/CLEC4F	81	80	73
INF vs Rest	APOL4/TLCD4	84	74	76	IFN vs Rest	LAMP3/TPPP3	81	76	73
INF vs Rest	APOL4/KLHDC8A	78	74	67	IFN vs Rest	LAMP3/LY6E	81	74	74
INF vs Rest	APOL4/SPTA1	83	71	77	IFN vs Rest	LAMP3/BATF2	90	84	77
INF vs Rest	APOL4/TSPAN5	86	78	78	IFN vs Rest	LAMP3/EXOC3L1	81	76	72
INF vs Rest	APOL4/GYPA	85	79	74	IFN vs Rest	LAMP3/HES4	86	80	76
INF vs Rest	APOL4/ITLN1	82	74	74	IFN vs Rest	APOL1/SEPTIN4	88	86	80
INF vs Rest	APOL4/RNF182	84	74	78	IFN vs Rest	APOL1/EPSTI1	91	84	78
INF vs Rest	APOL4/GLRX5	86	79	76	IFN vs Rest	APOL1/RSAD2	89	81	79
INF vs Rest	APOL4/RHCE	84	71	75	IFN vs Rest	APOL1/IFITM3	91	82	81
INF vs Rest	APOL4/THEM5	83	75	76	IFN vs Rest	APOL1/SERPING1	90	88	80
INF vs Rest	APOL4/IFIT1B	88	79	77	IFN vs Rest	APOL1/CLEC4F	89	87	80
INF vs Rest	RIOK3/BNIP3L	86	73	79	IFN vs Rest	APOL1/TPPP3	89	82	78
INF vs Rest	RIOK3/TFEC	87	77	80	IFN vs Rest	APOL1/LY6E	88	82	80
INF vs Rest	RIOK3/RHAG	85	68	79	IFN vs Rest	APOL1/BATF2	91	89	79
INF vs Rest	RIOK3/TSP02	84	67	78	IFN vs Rest	APOL1/EXOC3L1	89	81	80
INF vs Rest	RIOK3/CD274	82	70	77	IFN vs Rest	APOL1/HES4	88	82	80
INF vs Rest	RIOK3/TMCC2	86	69	79	IFN vs Rest	SEPTIN4/EPSTI1	88	84	72
INF vs Rest	RIOK3/CA1	88	79	79	IFN vs Rest	SEPTIN4/RSAD2	82	78	72
INF vs Rest	RIOK3/DYRK3	83	70	81	IFN vs Rest	SEPTIN4/IFITM3	87	79	79
INF vs Rest	RIOK3/FAM83A	86	74	78	IFN vs Rest	SEPTIN4/SERPING1	87	80	76
INF vs Rest	RIOK3/TLCD4	85	71	78	IFN vs Rest	SEPTIN4/CLEC4F	82	79	74
INF vs Rest	RIOK3/ANKRD22	82	68	78	IFN vs Rest	SEPTIN4/TPPP3	83	78	75
INF vs Rest	RIOK3/GBP5	83	67	77	IFN vs Rest	SEPTIN4/LY6E	81	76	75
INF vs Rest	RIOK3/KLHDC8A	83	66	74	IFN vs Rest	SEPTIN4/BATF2	89	86	77
INF vs Rest	RIOK3/SPTA1	84	71	81	IFN vs Rest	SEPTIN4/EXOC3L1	83	79	73
INF vs Rest	RIOK3/TSPAN5	86	75	79	IFN vs Rest	SEPTIN4/HES4	83	75	76
INF vs Rest	RIOK3/GYPA	86	70	77	IFN vs Rest	EPSTI1/RSAD2	87	84	70
INF vs Rest	RIOK3/P2RY14	82	66	78	IFN vs Rest	EPSTI1/IFITM3	89	85	75
INF vs Rest	RIOK3/ITLN1	85	70	79	IFN vs Rest	EPSTI1/SERPING1	89	85	75
INF vs Rest	RIOK3/RNF182	86	76	79	IFN vs Rest	EPSTI1/CLEC4F	87	84	71
INF vs Rest	RIOK3/GLRX5	86	75	75	IFN vs Rest	EPSTI1/TPPP3	88	87	73
INF vs Rest	RIOK3/RHCE	85	70	79	IFN vs Rest	EPSTI1/LY6E	91	88	73
INF vs Rest	RIOK3/THEM5	86	73	80	IFN vs Rest	EPSTI1/BATF2	91	83	76
INF vs Rest	RIOK3/IFIT1B	88	74	80	IFN vs Rest	EPSTI1/EXOC3L1	87	86	69
INF vs Rest	RIOK3/CARD17	82	68	75	IFN vs Rest	EPSTI1/HES4	89	86	76

INF vs Rest	BNIP3L/TFEC	89	80	81	INF vs Rest	RSAD2/IFITM3	83	80	73
INF vs Rest	BNIP3L/RHAG	87	75	79	INF vs Rest	RSAD2/SERPING1	86	81	74
INF vs Rest	BNIP3L/TSPO2	87	72	78	INF vs Rest	RSAD2/CLEC4F	77	72	66
INF vs Rest	BNIP3L/CD274	86	77	77	INF vs Rest	RSAD2/TPPP3	79	83	67
INF vs Rest	BNIP3L/TMCC2	87	75	78	INF vs Rest	RSAD2/LY6E	80	75	69
INF vs Rest	BNIP3L/CA1	88	80	78	INF vs Rest	RSAD2/BATF2	89	80	75
INF vs Rest	BNIP3L/DYRK3	86	73	77	INF vs Rest	RSAD2/EXOC3L1	78	74	67
INF vs Rest	BNIP3L/FAM83A	88	75	79	INF vs Rest	RSAD2/HES4	81	73	70
INF vs Rest	BNIP3L/TLCD4	87	72	79	INF vs Rest	IFITM3/SERPING1	89	83	77
INF vs Rest	BNIP3L/ANKRD22	86	76	75	INF vs Rest	IFITM3/CLEC4F	82	80	72
INF vs Rest	BNIP3L/GBP5	86	76	75	INF vs Rest	IFITM3/TPPP3	86	86	73
INF vs Rest	BNIP3L/KLHDC8A	86	78	77	INF vs Rest	IFITM3/LY6E	81	76	72
INF vs Rest	BNIP3L/SPTA1	87	76	80					
INF vs Rest	BNIP3L/TSPAN5	87	77	81	INF vs Rest	IFITM3/EXOC3L1	83	80	73
INF vs Rest	BNIP3L/GYP A	88	74	78	INF vs Rest	IFITM3/HES4	82	80	69
INF vs Rest	BNIP3L/P2RY14	86	76	77	INF vs Rest	SERPING1/CLEC4F	87	83	75
INF vs Rest	BNIP3L/TLN1	87	75	80	INF vs Rest	SERPING1/TPPP3	89	90	76
INF vs Rest	BNIP3L/RNF182	89	77	79	INF vs Rest	SERPING1/LY6E	87	83	76
INF vs Rest	BNIP3L/GLRX5	87	76	77	INF vs Rest	SERPING1/BATF2	90	87	76
INF vs Rest	BNIP3L/RHCE	88	75	80	INF vs Rest	SERPING1/EXOC3L1	87	84	74
INF vs Rest	BNIP3L/THEM5	89	77	80	INF vs Rest	SERPING1/HES4	88	84	74
INF vs Rest	BNIP3L/IFIT1B	89	78	81	INF vs Rest	CLEC4F/BATF2	88	87	75
INF vs Rest	BNIP3L/CARD17	86	76	76	INF vs Rest	CLEC4F/EXOC3L1	80	77	70
INF vs Rest	TFEC/RHAG	84	72	76	INF vs Rest	TPPP3/BATF2	89	86	75
INF vs Rest	TFEC/TSPO2	82	69	75	INF vs Rest	TPPP3/EXOC3L1	82	74	71
INF vs Rest	TFEC/TMCC2	84	71	75	INF vs Rest	LY6E/BATF2	88	81	76
INF vs Rest	TFEC/CA1	89	89	79	INF vs Rest	LY6E/EXOC3L1	80	74	72
INF vs Rest	TFEC/DYRK3	83	74	74	INF vs Rest	BATF2/EXOC3L1	89	85	76
INF vs Rest	TFEC/FAM83A	84	73	78	INF vs Rest	BATF2/HES4	88	84	76
INF vs Rest	TFEC/TLCD4	87	76	79	INF vs Rest	EXOC3L1/HES4	85	78	75
INF vs Rest	TFEC/KLHDC8A	79	70	70	ADA Endotype				
INF vs Rest	TFEC/SPTA1	85	71	79	ADA vs Rest	IGF1/LGALS3BP	86	76	82
INF vs Rest	TFEC/TSPAN5	88	80	82	ADA vs Rest	IGF1/OTOF	82	71	83
INF vs Rest	TFEC/GYP A	88	84	77	ADA vs Rest	TNFRSF17/LGALS3BP	86	73	82
INF vs Rest	TFEC/ITLN1	83	70	78	ADA vs Rest	TNFRSF17/OTOF	83	68	82
INF vs Rest	TFEC/RNF182	84	72	78	ADA vs Rest	GTSE1/LGALS3BP	87	76	84
INF vs Rest	TFEC/GLRX5	89	81	80	ADA vs Rest	GTSE1/OTOF	82	69	85
INF vs Rest	TFEC/RHCE	87	71	82	ADA vs Rest	CDC45/LGALS3BP	86	75	83
INF vs Rest	TFEC/THEM5	84	71	80	ADA vs Rest	CDC45/OTOF	83	69	85
INF vs Rest	TFEC/IFIT1B	90	81	81	ADA vs Rest	CAV1/LGALS3BP	85	74	81
INF vs Rest	RHAG/TSPO2	83	71	75	ADA vs Rest	CAV1/OTOF	81	70	82
INF vs Rest	RHAG/CD274	82	70	73	ADA vs Rest	LGALS3BP/GPRC5D	86	77	82
INF vs Rest	RHAG/TMCC2	84	73	76	ADA vs Rest	LGALS3BP/OTOF	88	78	86
INF vs Rest	RHAG/CA1	87	86	77	ADA vs Rest	LGALS3BP/SDC1	86	73	82
INF vs Rest	RHAG/DYRK3	83	71	75	ADA vs Rest	LGALS3BP/CENPF	87	79	83
INF vs Rest	RHAG/FAM83A	85	73	77	ADA vs Rest	LGALS3BP/KIF14	88	77	81
INF vs Rest	RHAG/TLCD4	85	77	78	ADA vs Rest	LGALS3BP/PLAAT2	87	75	81
INF vs Rest	RHAG/ANKRD22	82	69	73	ADA vs Rest	LGALS3BP/KCTD14	87	75	83
INF vs Rest	RHAG/GBP5	82	72	72	ADA vs Rest	LGALS3BP/PDIA4	87	76	84
INF vs Rest	RHAG/KLHDC8A	83	75	75	ADA vs Rest	LGALS3BP/SLC16A14	85	75	81

INF vs Rest	RHAG/SPTA1	85	70	77	ADA vs Rest	LGALS3BP/KIF15	86	76	83
INF vs Rest	RHAG/TSPAN5	87	76	80	ADA vs Rest	LGALS3BP/TSHR	87	76	82
INF vs Rest	RHAG/GYP A	86	73	76	ADA vs Rest	LGALS3BP/IFI27	88	78	82
INF vs Rest	RHAG/P2RY14	81	71	73	ADA vs Rest	LGALS3BP/MIXL1	86	74	83
INF vs Rest	RHAG/ITLN1	85	73	78	ADA vs Rest	LGALS3BP/KLHL14	86	77	82
INF vs Rest	RHAG/RNF182	86	79	79	ADA vs Rest	LGALS3BP/MIR155HG	85	73	82
INF vs Rest	RHAG/GLRX5	86	76	77	ADA vs Rest	LGALS3BP/IGLL5	86	77	80
INF vs Rest	RHAG/RHCE	85	76	78	ADA vs Rest	GPRC5D/OTOF	82	71	84
INF vs Rest	RHAG/THEM5	86	74	81	ADA vs Rest	OTOF/SDC1	81	71	82
INF vs Rest	RHAG/IFIT1B	89	79	81	ADA vs Rest	OTOF/CENPF	83	70	87
INF vs Rest	RHAG/CARD17	82	72	71	ADA vs Rest	OTOF/KIF14	83	74	82
INF vs Rest	TSPO2/CD274	81	70	71	ADA vs Rest	OTOF/PLAAT2	83	67	81
INF vs Rest	TSPO2/TMCC2	83	66	76	ADA vs Rest	OTOF/KCTD14	82	70	86
INF vs Rest	TSPO2/CA1	87	82	76	ADA vs Rest	OTOF/PDIA4	83	72	85
INF vs Rest	TSPO2/DYRK3	82	66	75	ADA vs Rest	OTOF/SLC16A14	82	69	84
INF vs Rest	TSPO2/FAM83A	85	76	78	ADA vs Rest	OTOF/KIF15	82	69	84
INF vs Rest	TSPO2/TLCD4	85	69	76	ADA vs Rest	OTOF/TSHR	83	70	82
INF vs Rest	TSPO2/ANKRD22	81	67	70	ADA vs Rest	OTOF/IFI27	87	76	86
INF vs Rest	TSPO2/GBP5	80	70	70	ADA vs Rest	OTOF/MIXL1	82	71	82
INF vs Rest	TSPO2/KLHDC8A	82	66	72	ADA vs Rest	OTOF/KLHL14	81	68	84
INF vs Rest	TSPO2/SPTA1	84	71	76	ADA vs Rest	OTOF/MIR155HG	81	69	83
INF vs Rest	TSPO2/TSPAN5	86	73	80	ADA vs Rest	OTOF/IGLL5	83	70	83
INF vs Rest	TSPO2/GYP A	85	72	76	ADA vs Rest	CENPF/KCTD14	76	61	75
INF vs Rest	TSPO2/P2RY14	80	68	72	ADA vs Rest	KIF14/KCTD14	77	58	75
INF vs Rest	TSPO2/ITLN1	83	67	77	ADA vs Rest	PLAAT2/KCTD14	76	66	76
INF vs Rest	TSPO2/RNF182	87	73	79	ADA vs Rest	KCTD14/PDIA4	77	63	76
INF vs Rest	TSPO2/GLRX5	86	77	76	ADA vs Rest	KCTD14/TSHR	75	62	77
					ADA vs Rest	KCTD14/KLHL14	75	66	73

Table 7: Severity and outcomes of the endotypes in the ICU cohort.

Parameter	Mechanistic Endotypes				P Val
	NPS (N=36)	INF (N=33)	IHD (N=6)	IFN (N=7)	
Covid-19 PCR Positivity	16.7% (6/36)	39.4% (13/33)	16.7% (1/6)	100% (7/7)	5.0e-4
Mortality within 28 Days	45.7% (16/35)	25.9% (7/27)	0% (0/5)	0% (0/6)	2.5e-2
SOFA 24H post ICU admission	7.6 ± 0.9 (34)	8.2 ± 0.78 (32)	3.5 ± 1.34 (6)	3.7 ± 1.49 (7)	3.3e-2
ICU Mortality	38.9% (14/36)	18.2% (6/33)	0% (0/6)	0% (0/5)	3.4e-2
ICU Stay Days	10.4 ± 1.29 (36)	15.2 ± 1.63 (33)	6.8 ± 2.7 (6)	9.7 ± 3.43 (7)	5.0e-2
SOFA 48H post admission	7.5 ± 0.98 (31)	8.4 ± 0.75 (30)	3.5 ± 0.87 (4)	4.1 ± 1.7 (7)	7.9e-2
SOFA at ICU admission	8.4 ± 0.9 (36)	7.9 ± 0.64 (33)	4.2 ± 1.7 (6)	5 ± 1.66 (7)	9.3e-2

The mean value ± standard error is presented for numerical variables with the total available observations/patient numbers recorded in brackets. Categorical variables are presented as percent positive (% total positive/total available observations). P values are derived from Wilcoxon and Chi squared tests testing for significant differences between endotypes for numerical and categorical values, respectively.

Table 8: Gene set for classifying patients into severity groups.

Gene Name	Description	Fold Change			
		High vs. Low	Int. vs. Low	High + Int. vs. Low	High vs. Int.
ABCA13	ATP binding cassette subfamily A member 13	1.67	-1.56	-1.06	2.62
ADAMTS2	ADAM metalloproteinase thrombospondin T1 M2	1.1	1.73	1.52	-1.57
ADAMTS3	ADAM metalloproteinase thrombospondin T1 M3	2.99	1.24	1.88	2.41
AK5*	adenylate kinase 5	-1.52	-1.37	-1.42	-1.11
ANKRD22*	ankyrin repeat domain 22	2.48	1.1	1.41	2.25
ANKRD34B	ankyrin repeat domain 34B	1.68	-1.05	1.17	1.78
ANLN	anillin actin binding protein	2.03	-1.48	1.03	3.01
AQP1	aquaporin 1 (Colton blood group)	1.66	-1.01	1.19	1.68
ARG1	arginase 1	1.11	1.31	1.25	-1.18
ARHGAP44	Rho GTPase activating protein 44	-4	-2.44	-2.36	-1.64
ARHGEF17*	Rho guanine nucleotide exchange factor 17	1.64	1.46	1.53	1.12
ASPM*	assembly factor for spindle microtubules	1.69	-1.91	-1.19	3.23
ATP1B2*	ATPase Na ⁺ /K ⁺ transporting subunit beta 2	1.96	1.09	1.37	1.79
AURKA*	aurora kinase A	1.63	-1.09	1.14	1.78
AZU1	azurocidin 1	1.89	-1.56	-1.02	2.95
BAIAP3*	BAI1 associated protein 3	-2.46	-1.25	-1.57	-1.97
BPI	bactericidal permeability increasing protein	2.17	-1.07	1.31	2.34
C1orf226*	chromosome 1 open reading frame 226	1.66	1.29	1.42	1.28
CACNB4*	calcium voltage-gated channel auxiliary SU β 4	-1.63	-1.15	-1.31	-1.41
CCL4L2* [#]	C-C motif chemokine ligand 4 like 2	40.32	5.19	1	7.77
CCN3*	cellular communication network factor 3	-2.35	-1.6	-1.82	-1.47
CCNA1	cyclin A1	1.56	1.82	1.72	-1.17
CD177*	CD177 molecule	1.85	1.38	1.51	1.34
CD24*	CD24 molecule	1.82	-1.38	1.04	2.51
CDK1	cyclin dependent kinase 1	2.1	-1.52	1.05	3.19
CDKN3	cyclin dependent kinase inhibitor 3	1.99	-1.25	1.16	2.5
CEACAM6	CEA cell adhesion molecule 6	2.06	-1.43	1.06	2.96
CEACAM8	CEA cell adhesion molecule 8	1.99	-1.4	1.09	2.8
CENPA*	centromere protein A	1.99	-1.3	1.15	2.59
CFH*	complement factor H	1.79	1.13	1.35	1.58
CHDH*	choline dehydrogenase	1.75	-1.25	1.07	2.19
CHIT1*	chitinase 1	1.39	1.11	1.2	1.24
CKAP2L*	cytoskeleton associated protein 2 like	2.23	-1.33	1.19	2.96
CLEC4C*	C-type lectin domain family 4 member C	-2.3	-1.13	-1.42	-2.04
CLEC4F	C-type lectin domain family 4 member F	-2.53	-1.78	-2.03	-1.43
CLNK	cytokine dependent hematopoietic cell linker	-2.59	-1.58	-1.78	-1.64

COL17A1	collagen type XVII alpha 1 chain	2.1	-1.25	1.16	2.62
CRISP2	cysteine rich secretory protein 2	2.48	1.76	1.98	1.41
CRISP3	cysteine rich secretory protein 3	1.97	1.44	1.61	1.37
CTSE	cathepsin E	1.59	1.33	1.41	1.2
CTSG	cathepsin G	2.03	-1.8	-1.07	3.66
CYP19A1	cytochrome P450 family 19 SF A member 1	2.38	1.08	1.38	2.2
CYYR1	cysteine and tyrosine rich 1	1.47	1.3	1.36	1.13
DEFA4	defensin alpha 4	2.27	-1.58	1.06	3.59
DENND2C*	DENN domain containing 2C	1.71	-1.24	1.08	2.13
DEPDC1	DEP domain containing 1	2.05	-2.01	-1.11	4.11
DGKK	diacylglycerol kinase kappa	-1.66	1	-1.24	-1.67
DLC1	DLC1 Rho GTPase activating protein	1.82	1.13	1.4	1.62
DLGAP5*	DLG associated protein 5	2.25	-1.51	1.07	3.39
DNAH10*	dynein axonemal heavy chain 10	1.81	1.06	1.32	1.71
DOC2B	double C2 domain beta	1.84	-1.29	1.1	2.37
DSP*	desmoplakin	-2.48	-1.73	-2.05	-1.43
ELANE	elastase, neutrophil expressed	2.39	-1.33	1.17	3.18
ERG	ETS transcription factor ERG	1.87	-1.13	1.21	2.12
FAM20A*	Golgi associated secretory pathway pseudokinase	1.58	1.07	1.21	1.47
FAM83A	family with sequence similarity 83 member A	2.73	1.8	1.66	1.51
FBN1*	fibrillin 1	1.5	-1.44	-1.13	2.16
FFAR3	free fatty acid receptor 3	2.02	1.42	1.62	1.42
G0S2*	G0/G1 switch 2	2.4	1.42	1.79	1.69
GGT5*#	gamma-glutamyltransferase 5	3.14	1.68	2.18	1.87
GLB1L2*	galactosidase beta 1 like 2	-1.52	-1.6	-1.57	1.05
GJB6	gap junction protein beta 6	1.96	1.27	1.5	1.55
GPR84*#	G protein-coupled receptor 84	2.93	1.81	2.27	1.62
GRAMD1C*	GRAM domain containing 1C	-1.97	-1.46	-1.61	-1.35
GYPA	glycophorin A (MNS blood group)	1.61	-1.64	-1.07	2.64
HBM*	hemoglobin subunit mu	2.17	1.41	1.67	1.54
HMGB3*	high mobility group box 3	1.53	-1.1	1.1	1.69
HP*	haptoglobin	2.4	1.52	1.8	1.58
HPGD	15-hydroxyprostaglandin dehydrogenase	1.32	1.24	1.27	1.06
HRK*#	harakiri, BCL2 interacting protein	-4.84	-1.94	-2.75	-2.49
IGLL1	immunoglobulin lambda like polypeptide 1	2.53	1.04	1.53	2.43
IL1R2	interleukin 1 receptor type 2	1.25	1.17	1.19	1.07
IL1RL1	interleukin 1 receptor like 1	1.4	-1.03	1.03	1.45
INHBA	inhibin subunit beta A	2.14	-1.52	1.08	3.25
IQGAP3*	IQ motif containing GTPase activating protein 3	2.63	-1.12	1.39	2.94
ITGA7	integrin subunit alpha 7	1.56	-1.25	1.04	1.96
ITGB4*	integrin subunit beta 4	-2.36	-2.18	-2.23	-1.08
KIF15*	kinesin family member 15	1.65	-1.68	-1.12	2.78

KIF20A	kinesin family member 20A	2.01	-1.37	1.07	2.74
KLF14	Kruppel like factor 14	1.56	1.22	1.34	1.28
LAMB3*	laminin subunit beta 3	1.98	1.4	1.58	1.41
LCN2*	lipocalin 2	2.35	-1.2	1.14	2.81
LGR4	Leu rich repeat cont. G protein-coupled receptor 4	2.03	-1.09	1.24	2.22
LPL*	lipoprotein lipase	-1	1.65	1.89	-1.65
LTF*	lactotransferrin	2.56	-1.04	1.38	2.65
MAFG*	MAF bZIP transcription factor G	1.42	1.27	1.32	1.12
MERTK*	MER proto-oncogene, tyrosine kinase	1.75	1.1	1.27	1.59
METTL7B	methyltransferase like 7B	1.58	1.12	1.26	1.41
MMP8*#	matrix metallopeptidase 8	4.37	-1.06	1.61	4.63
MMP9*	matrix metallopeptidase 9	1.45	1.36	1.39	1.06
MPO	myeloperoxidase	2.05	-1.37	1.09	2.82
MRC1*	mannose receptor C-type 1	1.95	1.81	2.45	1.08
MROCK1	cis-regulating promoter of cytokines inflammation	2.2	-1.16	1.48	2.55
MS4A3	membrane spanning 4-domains A3	1.91	-1.65	-1.03	3.15
MS4A4A*	membrane spanning 4-domains A4A	2.01	1.18	1.39	1.71
NECAB1	N-terminal EF-hand calcium binding protein 1	1.51	-1.33	1.01	2
NEIL3	nei like DNA glycosylase 3	2	-1.67	1	3.36
NEK2	NIMA related kinase 2	1.73	-1.7	-1.06	2.94
NRXN2*	neurexin 2	-1.93	-1.1	-1.34	-1.75
NUF2*	NUF2 component NDC80 kinetochore complex	1.51	-1.68	-1.15	2.53
OLAH	oleoyl-ACP hydrolase	1.42	1.52	1.49	-1.08
OLFM4	olfactomedin 4	2.26	-1.04	1.35	2.34
OLIG2	oligodendrocyte transcription factor 2	1.28	-1.84	-1.35	2.36
PCOLCE2	procollagen C-endopeptidase enhancer 2	2.5	-1.16	1.3	2.89
PCSK9	proprotein convertase subtilisin/kexin type 9	1.43	1.01	1.13	1.42
PHF24*	PHD finger protein 24	-2.85	1.13	-1.3	-3.23
PIGR	polymeric immunoglobulin receptor	-5.12	-3.66	-2.27	-1.4
PLAAT2	phospholipase A and acyltransferase 2	1.36	1.47	1.45	-1.08
PPARG	peroxisome proliferator activated receptor gamma	1.72	1.49	1.57	1.15
PRTN3	proteinase 3	2.65	-1.43	1.16	3.78
PTGES*	prostaglandin E synthase	1.69	1.59	1.62	1.06
PYCR1*	pyrroline-5-carboxylate reductase 1	1.72	-1.01	1.25	1.74
RAB3IL1*	RAB3A interacting protein like 1	1.4	-1.04	1.1	1.46
RASGRF1#	Ras protein specific guanine nucleotide RF1	-4.85	-1.17	-2.77	-4.15
RETN*	resistin	1.97	1.41	1.56	1.39
RHCE	Rh blood group CcEe antigens	1.63	-1.29	1.07	2.1
RIPOR3	RIPOR family member 3	1.82	-1.11	1.22	2.01
RPGRIP1*	RPGR interacting protein 1	-2.22	-1.41	-1.61	-1.57
RRM2*	ribonucleotide reductase regulatory subunit M2	2.29	-1.38	1.12	3.16
S100A12	S100 calcium binding protein A12	1.89	1.12	1.35	1.68

S100A8	S100 calcium binding protein A8	1.63	1.03	1.21	1.59
SCN8A*	sodium voltage-gated channel alpha subunit 8	2.02	-1.26	1.19	2.55
SEMA6B	semaphorin 6B	1.96	2.35	1.63	-1.2
SERPINB10*	serpin family B member 10	2.28	-1.14	1.29	2.6
SIGLEC8	sialic acid binding Ig like lectin 8	1.22	-2.3	-1.55	2.8
SIL1*	SIL1 nucleotide exchange factor	1.31	1.19	1.23	1.1
SLC16A1*	solute carrier family 16 member 1	1.55	-1.3	1.04	2.02
SLC28A3	solute carrier family 28 member 3	2.06	1.11	1.42	1.86
SLC39A8*	solute carrier family 39 member 8	2.64	1.39	1.81	1.9
SLC4A10*	solute carrier family 4 member 10	-2.64	-1.51	-1.83	-1.75
SLC51A	solute carrier family 51 subunit alpha	1.72	1.02	1.21	1.68
SLC6A19*	solute carrier family 6 member 19	2.5	1.87	2.06	1.34
SLC8A3*	solute carrier family 8 member A3	-1.93	-1.51	-1.66	-1.28
SLCO4A1	solute carrier organic anion transporter FM4A1	1.95	1.07	1.33	1.83
SMIM1*	small integral membrane protein 1 (Vel blood gp)	1.73	1.49	1.58	1.16
SMPDL3A	sphingomyelin phosphodiesterase acid like 3A	2.03	1.12	1.34	1.82
SPATC1*	spermatogenesis and centriole associated 1	2.33	1.44	1.7	1.62
SPOP*	speckle type BTB/POZ protein	-1.14	-1.06	-1.08	-1.08
SSBP2*	single stranded DNA binding protein 2	-1.34	-1.21	-1.25	-1.11
TCN1	transcobalamin 1	2.12	-1.1	1.28	2.34
TCTEX1D1*	Tctex1 domain containing 1	2.39	-1.14	1.31	2.73
TDRD9	tudor domain containing 9	1.68	1.04	1.22	1.61
TEAD2*	TEA domain transcription factor 2	-2.22	-1.38	-1.6	-1.6
TFRC	transferrin receptor	1.47	-1.39	-1.01	2.05
THBS1	thrombospondin 1	1.94	1.21	1.45	1.6
TIMP3	TIMP metalloproteinase inhibitor 3	1.33	-1.39	-1.1	1.85
TLN2*	talin 2	1.51	1.16	1.29	1.3
TMEM255A*	transmembrane protein 255A	-2.07	-1.32	-1.61	-1.56
TMEM45A*	transmembrane protein 45A	1.14	1.05	1.07	1.09
TNFAIP8L3	TNF alpha induced protein 8 like 3	2.28	1.22	1.58	1.87
TNIP3	TNFAIP3 interacting protein 3	1.75	1.07	1.34	1.63
TROAP	trophinin associated protein	1.75	-1.15	1.14	2.02
TTK	TTK protein kinase	2	-1.46	1.06	2.92
VSIG4	V-set and immunoglobulin domain containing 4	1.32	2.06	1.9	-1.56
WNT3	Wnt family member 3	-2.92	-1.03	-1.4	-2.83
YPEL4	yippee like 4	1.64	-1.24	1.12	2.03
ZDHHC19	zinc finger DHHC-type palmitoyltransferase 19	1.73	1.03	1.2	1.68

These 157 genes demonstrate differential expression between patients from different severity groups. Int. means intermediate. A reduced 73 gene set used for classifying patients into High vs. Low severity groups is indicated by * in column 1; these represent highly accurate and discriminative genes. A reduced signature presented in Table 8 is indicated by #.

Table 9: Severity model performance for three outcome measures predicting impending severity and mortality.

Comparison	Gene Set	Cross Validation Accuracy (AUC)/Sensitivity/Specificity (N = 194)
High vs. Low	High vs. Low all DE Genes	85%; 76%; 76%
	Reduced High vs Low DE Signature ^a	80%; 72%; 71%
	Hypothesis Based Signature ^b	77%; 73%; 73%
High + Intermediate vs. Low	High vs. Low DE Genes	79%; 65%; 75%
	Reduced High vs Low DE Signature ^a	70%; 70%; 69%
	Hypothesis Based Signature ^b	74%; 69%; 68%

The AUC, sensitivity, and specificity of the models, and the machine learning algorithm used is provided. DE = differentially expressed.

^a CCL4L2, GPR84, HRK, MMP8, GGT5, RASGRF1

^b ADAMTS2, RETN, MMP8, G0S2, CYP19A1, OLAH, SLC6A19, TNFAIP8L3

CLAIMS

What is claimed is:

1. A method for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising:

- (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and
- (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype,

wherein the sample gene signature and reference gene signature comprise an NPS endotype sub-signature, an INF endotype sub-signature, an IHD endotype sub-signature, an IFN endotype sub-signature, an ADA endotype sub-signature or combinations thereof,

wherein the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, ZDHHC19, ADAMTS3, AKR1C1, ALDH1A2, ALOX5AP, ALPL, AMPH, ANKRD55, BCL3, BTBD19, CA4, CD163L1, CD177, CD82, CST7, CYP19A1, CYSTM1, DAAM2, DGAT2, ECHDC3, ENTPD7, EXOSC4, FFAR3, FGF13, FSTL4, GALNT14, GRAMD1A, GRB10, GYG1, HPGD, IER3, IL18RAP, IL1R2, IL1RN, IRAG1-AS1, KCNE1B, KCNMA1, MCEMP1, MKNK1, MMP9, MSRA, NECAB1, NSMCE1-DT, OPLAH, PDGFC, PFKFB3, PHF24, PI3, PLIN4, PLIN5, PLK3, POR, PROK2, RFX2, RGL4, ROM1, S100A12, S100P, SEMA6B, SHROOM4, SLPI, SOCS3, SPATC1, SPDYA, SPINK8, SPP1, ST6GALNAC3, SYN2, TDRD9, TMEM120A, TMIGD3, TSPO, UPP1, and XCR1;

wherein the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYPA, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, TSPO2, ABCG2, ACHE, ACKR1, ACSL6, ADD2, AHSP, ALAS2, ALDH5A1, ANK1, ANKRD9, AQP1, ARHGEF12, ARHGEF37, ARL4A, ATP1B2, ATP1B2, BBOF1, BCAM, BCL2L1, BLVRB, BPGM, C1orf116, CA2, CISD2, CLIC2, CR1L, CR1L, CTNNAL1, CTSE, DCAF12, DMTN, DNAJC6, DPCD, DYRK3, EMID1, EPB42,

ERFE, FAM210B, FAXDC2, FRMD4A, GMPR, GSPT1, GYPB, HBM, HEMGN, HEPACAM2, HMBS, IGF2BP2, ISCA1, ITLN1, KANK2, KCNH2, KDM7A-DT, KEL, KLC3, KLF1, KLHDC8A, KRT1, LRRC2, MAOA, MARCHF8, MBNL3, MFSD2B, MRC2, MXI1, MYL4, NFIX, NUDT4, OSBP2, PAGE2B, PBX1, PCDH1, PGF, PLEK2, PNP, PRDX2, PTPRF, RAP1GAP, RBM38, RFESD, RFESD, RGCC, RGS16, RHAG, RHD, RIPOR3, RNF175, RUND3A, SEC14L4, SELENBP1, SELENOP, SFRP2, SGIP1, SIAH2, SLC14A1, SLC1A5, SLC22A23, SLC2A1, SLC4A1, SLC6A8, SLC6A9, SLC7A5, SMIM5, SNCA, SOX6, SPTB, STRADB, TAL1, TENT5C, TFR2, TMCC2, TMOD1, TNS1, TRIM10, TRIM58, TSPAN7, TTC25, UBB, USP12, XK, YBX3, and YPEL4;

wherein the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, ZNF600, ADGRD1, ANGPT1, GPR82, HDAC9, IL5RA, KLHDC1, PRSS33, PTGDR2, PTGFRN, TBC1D12, and TRIM2;

wherein the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, TFEC, EXOC3L1, IRF7, OAS1, SEPTIN4, LY6E, and LAMP3; and

wherein the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, USP18, AGRN, CD38, CDCA7, CDT1, CTLA4, DHX58, EME1, FAM111B, HES4, IFI44L, IFIT3, IFNG-AS1, IL12RB2, IL4I1, KIF19, LAG3, MCM10, P2RY6, PACSIN1, PARM1, SAMD4A, SPATS2L, HERC5, TMPRSS3, TNFRSF13B, TSHR, and TTC21A.

2. The method of claim 1, wherein the reference gene signature represents a standard level of expression of the genes comprised therein and a difference between a sample endotype sub-signature and a reference endotype sub-signature indicates that the subject has the sepsis mechanistic endotype corresponding to that sub-signature.

3. The method of claim 1 or 2, wherein the sample gene signature and the reference gene signature comprise the NPS endotype sub-signature, the INF endotype sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, and the ADA endotype sub-signature.
4. The method of any one of claims 1 to 3, wherein when the NPS endotype sub-signature comprises genes selected from the group consisting of: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19.
5. The method of claim 4, wherein the NPS endotype sub-signature comprises: AGFG1, ARG1, ATP9A, ANXA3, EFNA1, GADD45A, GPR84, HPGD, IL1R1, KLF14, KREMEN1, MIR646HG, MLLT1, NSUN7, OLAH, ORM2, PCOLCE2, PFKFB2, SLC51A, TNFAIP8L3, and ZDHHC19.
6. The method of any one of claims 1 to 5, wherein the INF endotype sub-signature comprises genes selected from the group consisting of: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2.
7. The method of claim 6, wherein the INF endotype sub-signature comprises: BNIP3L, CA1, FAM83A, FECH, GLRX5, GYP A, IFIT1B, RHCE, RIOK3, RNF182, SLC6A19, SPTA1, THEM5, TLCD4, TSPAN5, and TSPO2.
8. The method of any one of claims 1 to 7, wherein the IHD endotype sub-signature comprises genes selected from the group consisting of: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600.
9. The method of claim 8, wherein the IHD endotype sub-signature comprises: ABCA6, ADAM23, ALOX15, CACNA2D3, DYNC2H1, GPR34, GRAMD1C, LPL, MAP7, MIR155HG, PLCB1, SDC2, SIGLEC8, SPRED1, SLC16A14, SMPD3, TPPP3, TPRG1, and ZNF600.

10. The method of any one of claims 1 to 9, wherein the IFN endotype sub-signature comprises genes selected from the group consisting of: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC.
11. The method of claim 10, wherein the IFN endotype sub-signature comprises: ANKRD22, APOL1, APOL4, BATF2, CARD17, CD274, EPSTI1, ETV7, GBP5, IDO1, IFITM3, P2RY14, PLEKHO1, RSAD2, SERPING1, and TFEC.
12. The method of any one of claims 1 to 11, wherein the ADA endotype sub-signature comprises genes selected from the group consisting of: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1, and USP18.
13. The method of claim 12, wherein the ADA endotype sub-signature comprises: CCL2, CDC45, CENPF, CLEC4F, GTSE1, IFI27, ISG15, KCTD14, KIF14, KIF15, KLHDC7B, LGALS3BP, OTOF, PDIA4, SIGLEC1 and USP18.
14. A method for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising:
 - (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and
 - (b) comparing the sample gene signature with a reference gene signature to determine whether the subject has the sepsis mechanistic endotype,
 wherein the sample gene signature and reference gene signature comprise an NPS endotype signature pair, an INF endotype signature pair, an IHD endotype signature pair, an IFN endotype signature pair, an ADA endotype signature pair or combinations thereof,

wherein the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14,

EFNA1/PFKFB2, MLLT1/KLF14, ADAMTS3/PCOLCE2, ADAMTS3/ZDHHC19,
 ADAMTS3/SLC51A, ADAMTS3/HPGD, ADAMTS3/SEMA6B, ADAMTS3/EFNA1,
 ADAMTS3/AGFG1, ADAMTS3/NSUN7, ADAMTS3/TNFAIP8L3,
 ADAMTS3/KREMEN1, ADAMTS3/ORM2, ADAMTS3/MIR646HG,
 ADAMTS3/KLF14, AGFG1/NSUN7, AGFG1/TNFAIP8L3, AGFG1/KREMEN1,
 AGFG1/ORM2, AGFG1/MIR646HG, AGFG1/KLF14, ANXA3/GPR84,
 ANXA3/OLAH, ANXA3/ADAMTS3, ANXA3/PCOLCE2, ANXA3/ZDHHC19,
 ANXA3/SLC51A, ANXA3/HPGD, ANXA3/SEMA6B, ANXA3/EFNA1,
 ANXA3/AGFG1, ANXA3/NSUN7, ANXA3/TNFAIP8L3, ANXA3/KREMEN1,
 ANXA3/ORM2, ANXA3/MIR646HG, ANXA3/KLF14, ARG1/PFKFB2,
 ARG1/MLLT1, ARG1/ANXA3, ARG1/GPR84, ARG1/OLAH, ARG1/ADAMTS3,
 ARG1/PCOLCE2, ARG1/ZDHHC19, ARG1/SLC51A, ARG1/HPGD,
 ARG1/SEMA6B, ARG1/EFNA1, ARG1/AGFG1, ARG1/NSUN7, ARG1/TNFAIP8L3,
 ARG1/KREMEN1, ARG1/ORM2, ARG1/MIR646HG, ARG1/KLF14,
 ATP9A/EPB41L4B, ATP9A/IL1R1, ATP9A/GADD45A, ATP9A/ARG1,
 ATP9A/PFKFB2, ATP9A/MLLT1, ATP9A/ANXA3, ATP9A/GPR84, ATP9A/OLAH,
 ATP9A/ADAMTS3, ATP9A/PCOLCE2, ATP9A/ZDHHC19, ATP9A/SLC51A,
 ATP9A/HPGD, ATP9A/SEMA6B, ATP9A/EFNA1, ATP9A/AGFG1,
 ATP9A/NSUN7, ATP9A/TNFAIP8L3, ATP9A/KREMEN1, ATP9A/ORM2,
 ATP9A/MIR646HG, ATP9A/KLF14, EFNA1/AGFG1, EFNA1/NSUN7,
 EFNA1/TNFAIP8L3, EFNA1/KREMEN1, EFNA1/ORM2, EFNA1/MIR646HG,
 EFNA1/KLF14, EPB41L4B/IL1R1, EPB41L4B/GADD45A, EPB41L4B/ARG1,
 EPB41L4B/PFKFB2, EPB41L4B/MLLT1, EPB41L4B/ANXA3, EPB41L4B/GPR84,
 EPB41L4B/OLAH, EPB41L4B/ADAMTS3, EPB41L4B/PCOLCE2,
 EPB41L4B/ZDHHC19, EPB41L4B/SLC51A, EPB41L4B/HPGD,
 EPB41L4B/SEMA6B, EPB41L4B/EFNA1, EPB41L4B/AGFG1, EPB41L4B/NSUN7,
 EPB41L4B/TNFAIP8L3, EPB41L4B/KREMEN1, EPB41L4B/MIR646HG,
 EPB41L4B/KLF14, GADD45A/ARG1, GADD45A/PFKFB2, GADD45A/MLLT1,
 GADD45A/ANXA3, GADD45A/GPR84, GADD45A/OLAH, GADD45A/ADAMTS3,
 GADD45A/PCOLCE2, GADD45A/ZDHHC19, GADD45A/SLC51A,
 GADD45A/HPGD, GADD45A/SEMA6B, GADD45A/EFNA1, GADD45A/AGFG1,
 GADD45A/NSUN7, GADD45A/TNFAIP8L3, GADD45A/KREMEN1,
 GADD45A/ORM2, GADD45A/MIR646HG, GADD45A/KLF14, GPR84/OLAH,

GPR84/ADAMTS3, GPR84/PCOLCE2, GPR84/ZDHHC19, GPR84/SLC51A,
 GPR84/HPGD, GPR84/SEMA6B, GPR84/EFNA1, GPR84/AGFG1, GPR84/NSUN7,
 GPR84/TNFAIP8L3, GPR84/KREMEN1, GPR84/ORM2, GPR84/MIR646HG,
 GPR84/KLF14, HPGD/SEMA6B, HPGD/EFNA1, HPGD/AGFG1, HPGD/NSUN7,
 HPGD/TNFAIP8L3, HPGD/KREMEN1, HPGD/ORM2, HPGD/MIR646HG,
 HPGD/KLF14, IL1R1/GADD45A, IL1R1/ARG1, IL1R1/PFKFB2, IL1R1/MLLT1,
 IL1R1/ANXA3, IL1R1/GPR84, IL1R1/OLAH, IL1R1/ADAMTS3, IL1R1/PCOLCE2,
 IL1R1/ZDHHC19, IL1R1/SLC51A, IL1R1/HPGD, IL1R1/SEMA6B, IL1R1/EFNA1,
 IL1R1/AGFG1, IL1R1/NSUN7, IL1R1/TNFAIP8L3, IL1R1/KREMEN1,
 IL1R1/ORM2, IL1R1/MIR646HG, IL1R1/KLF14, KREMEN1/ORM2,
 KREMEN1/MIR646HG, KREMEN1/KLF14, MIR646HG/KLF14, MLLT1/ANXA3,
 MLLT1/GPR84, MLLT1/OLAH, MLLT1/ADAMTS3, MLLT1/PCOLCE2,
 MLLT1/ZDHHC19, MLLT1/SLC51A, MLLT1/HPGD, MLLT1/SEMA6B,
 MLLT1/EFNA1, MLLT1/AGFG1, MLLT1/NSUN7, MLLT1/TNFAIP8L3,
 MLLT1/KREMEN1, MLLT1/ORM2, MLLT1/MIR646HG, MLLT1/KLF14,
 NSUN7/TNFAIP8L3, NSUN7/KREMEN1, NSUN7/ORM2, NSUN7/MIR646HG,
 NSUN7/KLF14, OLAH/ADAMTS3, OLAH/PCOLCE2, OLAH/ZDHHC19,
 OLAH/SLC51A, OLAH/HPGD, OLAH/SEMA6B, OLAH/EFNA1, OLAH/AGFG1,
 OLAH/NSUN7, OLAH/TNFAIP8L3, OLAH/KREMEN1, OLAH/ORM2,
 OLAH/MIR646HG, OLAH/KLF14, ORM2/MIR646HG, ORM2/KLF14,
 PCOLCE2/ZDHHC19, PCOLCE2/SLC51A, PCOLCE2/HPGD, PCOLCE2/SEMA6B,
 PCOLCE2/EFNA1, PCOLCE2/AGFG1, PCOLCE2/NSUN7, PCOLCE2/TNFAIP8L3,
 PCOLCE2/KREMEN1, PCOLCE2/ORM2, PCOLCE2/MIR646HG,
 PCOLCE2/KLF14, PFKFB2/MLLT1, PFKFB2/ANXA3, PFKFB2/GPR84,
 PFKFB2/OLAH, PFKFB2/ADAMTS3, PFKFB2/PCOLCE2, PFKFB2/ZDHHC19,
 PFKFB2/SLC51A, PFKFB2/HPGD, PFKFB2/SEMA6B, PFKFB2/EFNA1,
 PFKFB2/AGFG1, PFKFB2/NSUN7, PFKFB2/TNFAIP8L3, PFKFB2/KREMEN1,
 PFKFB2/ORM2, PFKFB2/MIR646HG, PFKFB2/KLF14, SEMA6B/EFNA1,
 SEMA6B/AGFG1, SEMA6B/NSUN7, SEMA6B/TNFAIP8L3, SEMA6B/KREMEN1,
 SEMA6B/ORM2, SEMA6B/MIR646HG, SEMA6B/KLF14, SLC51A/HPGD,
 SLC51A/SEMA6B, SLC51A/EFNA1, SLC51A/AGFG1, SLC51A/NSUN7,
 SLC51A/TNFAIP8L3, SLC51A/KREMEN1, SLC51A/ORM2, SLC51A/MIR646HG,
 SLC51A/KLF14, TNFAIP8L3/KREMEN1, TNFAIP8L3/ORM2,

TNFAIP8L3/MIR646HG, TNFAIP8L3/KLF14, ZDHHC19/SLC51A, ZDHHC19/HPGD, ZDHHC19/SEMA6B, ZDHHC19/EFNA1, ZDHHC19/AGFG1, ZDHHC19/NSUN7, ZDHHC19/TNFAIP8L3, ZDHHC19/KREMEN1, ZDHHC19/ORM2, ZDHHC19/MIR646HG, and ZDHHC19/KLF14;

wherein the INF endotype signature pair is selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, SPTA1/FECH, ANKRD22/GLRX5, ANKRD22/GYP A, ANKRD22/IFIT1B, ANKRD22/ITLN1, ANKRD22/KLHDC8A, ANKRD22/RHCE, ANKRD22/RNF182, ANKRD22/SPTA1, ANKRD22/THEM5, ANKRD22/TSPAN5, APOL4/BNIP3L, APOL4/CA1, APOL4/DYRK3, APOL4/FAM83A, APOL4/GLRX5, APOL4/GYP A, APOL4/IFIT1B, APOL4/ITLN1, APOL4/KLHDC8A, APOL4/RHAG, APOL4/RHCE, APOL4/RIOK3, APOL4/RNF182, APOL4/SPTA1, APOL4/THEM5, APOL4/TLCD4, APOL4/TMCC2, APOL4/TSPAN5, APOL4/TSPO2, BNIP3L/ANKRD22, BNIP3L/CA1, BNIP3L/CARD17, BNIP3L/CD274, BNIP3L/DYRK3, BNIP3L/FAM83A, BNIP3L/GBP5, BNIP3L/GLRX5, BNIP3L/GYP A, BNIP3L/IFIT1B, BNIP3L/ITLN1, BNIP3L/KLHDC8A, BNIP3L/P2RY14, BNIP3L/RHAG, BNIP3L/RHCE, BNIP3L/RNF182, BNIP3L/SPTA1, BNIP3L/TFEC, BNIP3L/THEM5, BNIP3L/TLCD4, BNIP3L/TMCC2, BNIP3L/TSPAN5, BNIP3L/TSPO2, CA1/ANKRD22, CA1/CARD17, CA1/DYRK3, CA1/FAM83A, CA1/GBP5, CA1/GLRX5, CA1/GYP A, CA1/IFIT1B, CA1/ITLN1, CA1/KLHDC8A, CA1/P2RY14, CA1/RHCE, CA1/RNF182, CA1/SPTA1, CA1/THEM5, CA1/TLCD4, CA1/TSPAN5, CD274/CA1, CD274/DYRK3, CD274/FAM83A, CD274/GLRX5, CD274/GYP A, CD274/IFIT1B, CD274/ITLN1, CD274/KLHDC8A, CD274/RHCE, CD274/RNF182, CD274/SPTA1, CD274/THEM5, CD274/TLCD4, CD274/TMCC2, CD274/TSPAN5, DYRK3/ANKRD22, DYRK3/CARD17, DYRK3/FAM83A, DYRK3/GBP5, DYRK3/GLRX5, DYRK3/GYP A, DYRK3/IFIT1B, DYRK3/ITLN1, DYRK3/KLHDC8A, DYRK3/P2RY14, DYRK3/RHCE, DYRK3/RNF182, DYRK3/SPTA1, DYRK3/THEM5, DYRK3/TLCD4, DYRK3/TSPAN5, FAM83A/ANKRD22, FAM83A/CARD17, FAM83A/GBP5, FAM83A/GLRX5, FAM83A/GYP A, FAM83A/IFIT1B, FAM83A/ITLN1, FAM83A/KLHDC8A, FAM83A/P2RY14, FAM83A/RHCE, FAM83A/RNF182, FAM83A/SPTA1, FAM83A/THEM5,

FAM83A/TLCD4, FAM83A/TSPAN5, FECH/ANKRD22, FECH/APOL4,
 FECH/BNIP3L, FECH/CA1, FECH/CARD17, FECH/CD274, FECH/DYRK3,
 FECH/FAM83A, FECH/GBP5, FECH/GLRX5, FECH/GYP A, FECH/IFIT1B,
 FECH/ITLN1, FECH/KLHDC8A, FECH/P2RY14, FECH/RHAG, FECH/RHCE,
 FECH/RIOK3, FECH/RNF182, FECH/SPTA1, FECH/TFEC, FECH/THEM5,
 FECH/TLCD4, FECH/TMCC2, FECH/TSPAN5, FECH/TSP02, GBP5/GLRX5,
 GBP5/GYP A, GBP5/IFIT1B, GBP5/ITLN1, GBP5/KLHDC8A, GBP5/RHCE,
 GBP5/RNF182, GBP5/SPTA1, GBP5/THEM5, GBP5/TSPAN5, GLRX5/CARD17,
 GLRX5/IFIT1B, GLRX5/RHCE, GLRX5/THEM5, GYP A/CARD17, GYP A/GLRX5,
 GYP A/IFIT1B, GYP A/ITLN1, GYP A/P2RY14, GYP A/RHCE, GYP A/RNF182,
 GYP A/THEM5, IFIT1B/CARD17, ITLN1/CARD17, ITLN1/GLRX5, ITLN1/IFIT1B,
 ITLN1/RHCE, ITLN1/RNF182, ITLN1/THEM5, KLHDC8A/CARD17,
 KLHDC8A/GLRX5, KLHDC8A/GYP A, KLHDC8A/IFIT1B, KLHDC8A/ITLN1,
 KLHDC8A/P2RY14, KLHDC8A/RHCE, KLHDC8A/RNF182, KLHDC8A/SPTA1,
 KLHDC8A/THEM5, KLHDC8A/TSPAN5, P2RY14/GLRX5, P2RY14/IFIT1B,
 P2RY14/ITLN1, P2RY14/RHCE, P2RY14/RNF182, P2RY14/THEM5,
 RHAG/ANKRD22, RHAG/CA1, RHAG/CARD17, RHAG/CD274, RHAG/DYRK3,
 RHAG/FAM83A, RHAG/GBP5, RHAG/GLRX5, RHAG/GYP A, RHAG/IFIT1B,
 RHAG/ITLN1, RHAG/KLHDC8A, RHAG/P2RY14, RHAG/RHCE, RHAG/RNF182,
 RHAG/SPTA1, RHAG/THEM5, RHAG/TLCD4, RHAG/TMCC2, RHAG/TSPAN5,
 RHAG/TSP02, RHCE/CARD17, RHCE/IFIT1B, RHCE/THEM5, RIOK3/ANKRD22,
 RIOK3/BNIP3L, RIOK3/CA1, RIOK3/CARD17, RIOK3/CD274, RIOK3/DYRK3,
 RIOK3/FAM83A, RIOK3/GBP5, RIOK3/GLRX5, RIOK3/GYP A, RIOK3/IFIT1B,
 RIOK3/ITLN1, RIOK3/KLHDC8A, RIOK3/P2RY14, RIOK3/RHAG, RIOK3/RHCE,
 RIOK3/RNF182, RIOK3/SPTA1, RIOK3/TFEC, RIOK3/THEM5, RIOK3/TLCD4,
 RIOK3/TMCC2, RIOK3/TSPAN5, RIOK3/TSP02, RNF182/CARD17,
 RNF182/GLRX5, RNF182/IFIT1B, RNF182/RHCE, RNF182/THEM5,
 SPTA1/CARD17, SPTA1/GLRX5, SPTA1/GYP A, SPTA1/IFIT1B, SPTA1/ITLN1,
 SPTA1/P2RY14, SPTA1/RHCE, SPTA1/RNF182, SPTA1/THEM5, SPTA1/TSPAN5,
 TFEC/CA1, TFEC/DYRK3, TFEC/FAM83A, TFEC/GLRX5, TFEC/GYP A,
 TFEC/IFIT1B, TFEC/ITLN1, TFEC/KLHDC8A, TFEC/RHAG, TFEC/RHCE,
 TFEC/RNF182, TFEC/SPTA1, TFEC/THEM5, TFEC/TLCD4, TFEC/TMCC2,
 TFEC/TSPAN5, TFEC/TSP02, THEM5/CARD17, THEM5/IFIT1B,

TLCD4/ANKRD22, TLCD4/CARD17, TLCD4/GBP5, TLCD4/GLRX5, TLCD4/GYPA, TLCD4/IFIT1B, TLCD4/ITLN1, TLCD4/KLHDC8A, TLCD4/P2RY14, TLCD4/RHCE, TLCD4/RNF182, TLCD4/SPTA1, TLCD4/THEM5, TLCD4/TSPAN5, TMCC2/ANKRD22, TMCC2/CA1, TMCC2/CARD17, TMCC2/DYRK3, TMCC2/FAM83A, TMCC2/GBP5, TMCC2/GLRX5, TMCC2/GYPA, TMCC2/IFIT1B, TMCC2/ITLN1, TMCC2/KLHDC8A, TMCC2/P2RY14, TMCC2/RHCE, TMCC2/RNF182, TMCC2/SPTA1, TMCC2/THEM5, TMCC2/TLCD4, TMCC2/TSPAN5, TSPAN5/CARD17, TSPAN5/GLRX5, TSPAN5/GYPA, TSPAN5/IFIT1B, TSPAN5/ITLN1, TSPAN5/P2RY14, TSPAN5/RHCE, TSPAN5/RNF182, TSPAN5/THEM5, TSPO2/ANKRD22, TSPO2/CA1, TSPO2/CARD17, TSPO2/CD274, TSPO2/DYRK3, TSPO2/FAM83A, TSPO2/GBP5, TSPO2/GLRX5, TSPO2/GYPA, TSPO2/IFIT1B, TSPO2/ITLN1, TSPO2/KLHDC8A, TSPO2/P2RY14, TSPO2/RHCE, TSPO2/RNF182, TSPO2/SPTA1, TSPO2/THEM5, TSPO2/TLCD4, TSPO2/TMCC2, and TSPO2/TSPAN5;

wherein the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, CACNA2D3/SPRED1, ADAM23/GPR34, ADAM23/MAP7, ADAM23/PLCB1, ADAM23/SPRED1, ALOX15/GPR34, ALOX15/PLCB1, ALOX15/SPRED1, BAALC/GPR34, BAALC/PLCB1, BAALC/SPRED1, CACNA2D3/DYNC2H1, CACNA2D3/GPR34, CACNA2D3/PLCB1, CACNA2D3/SPRED1, CACNA2D3/ZNF600, GPR34/DYNC2H1, GPR34/GRAMD1C, GPR34/PLCB1, GPR34/TPRG1, GPR34/ZNF600, GPR82/DYNC2H1, GPR82/GPR34, GPR82/GRAMD1C, GPR82/PLCB1, GPR82/TPRG1, GPR82/ZNF600, GRAMD1C/DYNC2H1, GRAMD1C/PLCB1, GRAMD1C/ZNF600, HRK/DYNC2H1, HRK/GPR34, HRK/MAP7, HRK/PLCB1, HRK/SPRED1, HRK/ZNF600, IL5RA/DYNC2H1, IL5RA/GPR34, IL5RA/PLCB1, IL5RA/SPRED1, IL5RA/TRIM2, MAP7/BAALC, MAP7/CACNA2D3, MAP7/DYNC2H1, MAP7/GPR34, MAP7/GPR82, MAP7/GRAMD1C, MAP7/PLCB1, MAP7/SPRED1, MAP7/TPRG1, MAP7/ZNF600, PLCB1/DYNC2H1, PLCB1/TPRG1, PLCB1/ZNF600, PRSS33/GPR34, PRSS33/PLCB1, PRSS33/SPRED1, SDC2/DYNC2H1, SDC2/GPR34, SDC2/PLCB1, SDC2/ZNF600,

SIGLEC8/DYNC2H1, SIGLEC8/GPR34, SIGLEC8/MAP7, SIGLEC8/PLCB1, SIGLEC8/SPRED1, SIGLEC8/TRIM2, SMPD3/DYNC2H1, SMPD3/GPR34, SMPD3/MAP7, SMPD3/PLCB1, SMPD3/SPRED1, SMPD3/TRIM2, SPRED1/DYNC2H1, SPRED1/GPR34, SPRED1/GPR82, SPRED1/GRAMD1C, SPRED1/PLCB1, SPRED1/SDC2, SPRED1/TPRG1, SPRED1/ZNF600, TRIM2/CACNA2D3, TRIM2/DYNC2H1, TRIM2/GPR34, TRIM2/GPR82, TRIM2/GRAMD1C, TRIM2/HRK, TRIM2/MAP7, TRIM2/PLCB1, TRIM2/SDC2, TRIM2/SPRED1, TRIM2/TPRG1, and TRIM2/ZNF600;

wherein the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, LAMP3/SERPING1, APOL1/BATF2, APOL1/CLEC4F, APOL1/EPSTI1, APOL1/EXOC3L1, APOL1/HES4, APOL1/IFITM3, APOL1/LY6E, APOL1/RSAD2, APOL1/SEPTIN4, APOL1/SERPING1, APOL1/TPPP3, BATF2/EXOC3L1, BATF2/HES4, CLEC4F/BATF2, CLEC4F/EXOC3L1, EPSTI1/BATF2, EPSTI1/CLEC4F, EPSTI1/EXOC3L1, EPSTI1/HES4, EPSTI1/IFITM3, EPSTI1/LY6E, EPSTI1/RSAD2, EPSTI1/SERPING1, EPSTI1/TPPP3, ETV7/APOL1, ETV7/BATF2, ETV7/CLEC4F, ETV7/EPSTI1, ETV7/EXOC3L1, ETV7/HES4, ETV7/IFITM3, ETV7/LAMP3, ETV7/LY6E, ETV7/PLEKHO1, ETV7/RSAD2, ETV7/SEPTIN4, ETV7/SERPING1, ETV7/TPPP3, EXOC3L1/HES4, IFITM3/SERPING1, IFITM3/CLEC4F, IFITM3/TPPP3, IFITM3/LY6E, IFITM3/EXOC3L1, IFITM3/HES4, LAMP3/APOL1, LAMP3/BATF2, LAMP3/CLEC4F, LAMP3/EPSTI1, LAMP3/EXOC3L1, LAMP3/HES4, LAMP3/IFITM3, LAMP3/LY6E, LAMP3/RSAD2, LAMP3/SEPTIN4, LAMP3/SERPING1, LAMP3/TPPP3, LY6E/BATF2, LY6E/EXOC3L1, PLEKHO1/APOL1, PLEKHO1/BATF2, PLEKHO1/EPSTI1, PLEKHO1/EXOC3L1, PLEKHO1/IFITM3, PLEKHO1/LAMP3, PLEKHO1/RSAD2, PLEKHO1/SEPTIN4, PLEKHO1/SERPING1, RSAD2/BATF2, RSAD2/CLEC4F, RSAD2/EXOC3L1, RSAD2/HES4, RSAD2/IFITM3, RSAD2/LY6E, RSAD2/SERPING1, RSAD2/TPPP3, SEPTIN4/BATF2, SEPTIN4/CLEC4F, SEPTIN4/EPSTI1, SEPTIN4/EXOC3L1, SEPTIN4/HES4, SEPTIN4/IFITM3, SEPTIN4/LY6E, SEPTIN4/RSAD2, SEPTIN4/SERPING1, SEPTIN4/TPPP3, SERPING1/BATF2, SERPING1/CLEC4F,

SERPING1/EXOC3L1, SERPING1/HES4, SERPING1/LY6E, SERPING1/TPPP3, TPPP3/BATF2, and TPPP3/EXOC3L1; and

wherein the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, LGALS3BP/MIXL, CAV1/LGALS3BP, CAV1/OTOF, CDC45/LGALS3BP, CDC45/OTOF, CENPF/KCTD14, GPRC5D/OTOF, GTSE1/LGALS3BP, GTSE1/OTOF, IGF1/LGALS3BP, IGF1/OTOF, KCTD14/KLHL14, KCTD14/PDIA4, KCTD14/TSHR, KIF14/KCTD14, LGALS3BP/CENPF, LGALS3BP/GPRC5D, LGALS3BP/IFI27, LGALS3BP/IGLL5, LGALS3BP/KCTD14, LGALS3BP/KIF14, LGALS3BP/KIF15, LGALS3BP/KLHL14, LGALS3BP/MIR155HG, LGALS3BP/MIXL1, LGALS3BP/OTOF, LGALS3BP/PDIA4, LGALS3BP/PLAAT2, LGALS3BP/SDC1, LGALS3BP/SLC16A14, LGALS3BP/TSHR, OTOF/CENPF, OTOF/IFI27, OTOF/IGLL5, OTOF/KCTD14, OTOF/KIF14, OTOF/KIF15, OTOF/KLHL14, OTOF/MIR155HG, OTOF/MIXL1, OTOF/PDIA4, OTOF/PLAAT2, OTOF/SDC1, OTOF/SLC16A14, OTOF/TSHR, PLAAT2/KCTD14, TNFRSF17/LGALS3BP, and TNFRSF17/OTOF.

15. The method of claim 14, wherein the reference gene signature represents a standard level of expression of the genes comprised therein and a difference between a sample endotype signature pair and a reference endotype signature pair indicates that the subject has the sepsis mechanistic endotype corresponding to that signature pair.
16. The method of claim 14 or 15, wherein the sample gene signature and the reference gene signature comprise the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, and the ADA endotype signature pair.
17. The method of any one of claims 14 to 16, wherein the NPS endotype signature pair is selected from: GADD45A/EFNA1, EFNA1/MIR646HG, MIR646HG/KLF14, MLLT1/MIR646HG, ARG1/MLLT1, MLLT1/EFNA1, MLLT1/NSUN7, EFNA1/NSUN7, SLC51A/EFNA1, EFNA1/KLF14, ZDHHC19/EFNA1, EFNA1/AGFG1, NSUN7/KLF14, EFNA1/PFKFB2, and MLLT1/KLF14.

18. The method of any one of claims 14 to 17, wherein the INF endotype signature pair is selected from: FECH/TFEC, TFEC/IFIT1B, FECH/RNF182, IFIT1B/FECH, FECH/APOL4, FECH/GYP A, ITLN1/FECH, FECH/THEM5, IFIT1B/CA1, RHAG/FECH, FECH/FAM83A, RHCE/FECH, TFEC/CA1, and SPTA1/FECH.
19. The method of any one of claims 14 to 18, wherein the IHD endotype signature pair is selected from: MAP7/SPRED1, SPRED1/GPR34, IL5RA/SPRED1, SPRED1/TPRG1, HRK/SPRED1, SPRED1/PLCB1, TRIM2/SPRED1, SIGLEC8/SPRED1, SMPD3/SPRED1, SPRED1/ZNF600, SPRED1/SDC2, MAP7/GPR34, PRSS33/SPRED1, SPRED1/DYNC2H1, and CACNA2D3/SPRED1.
20. The method of any one of claims 14 to 19, wherein the IFN endotype signature pair is selected from: ETV7/PLEKHO1, IFITM3/ETV7, ETV7/APOL1, BATF2/ETV7, PLEKHO1/BATF2, ETV7/EPSTI1, EPSTI1/BATF2, IFITM3/BATF2, USP18/EPSTI1, ETV7/SEPTIN4, ETV7/LAMP3, SERPING1/BATF2, LAMP3/BATF2, and LAMP3/SERPING1.
21. The method of any one of claims 14 to 20, wherein the ADA endotype signature pair is selected from: LGALS3BP/OTOF, LGALS3BP/IFI27, LGALS3BP/KIF14, LGALS3BP/CENPF, GTSE1/LGALS3BP, LGALS3BP/KCTD14, LGALS3BP/PDIA4, LGALS3BP/TSHR, LGALS3BP/PLAAT2, OTOF/IFI27, IGF1/LGALS3BP, CDC45/LGALS3BP, LGALS3BP/KIF15, LGALS3BP/IGLL5, and LGALS3BP/MIXL1.
22. A method for predicting severity of sepsis in a subject, wherein the severity of the sepsis is selected from high severity sepsis, intermediate severity sepsis and low severity sepsis, the method comprising:
 - (a) determining, in a biological sample from the subject, a level of expression for each of a plurality of genes, to provide a sample gene signature; and
 - (b) comparing the sample gene signature with a reference gene signature to predict the severity of the sepsis in the subject,

wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5, and low severity sepsis means a SOFA score of less than 2; and

wherein the plurality of genes is selected from the group consisting of ABCA13, ADAMTS2, ADAMTS3, AK5, ANKRD22, ANKRD34B, ANLN, AQP1, ARG1, ARHGAP44, ARHGEF17, ASPM, ATP1B2, AURKA, AZU1, BAIAP3, BPI, C1orf226, CACNB4, CCL4L2, CCN3, CCNA1, CD177, CD24, CDK1, CDKN3, CEACAM6, CEACAM8, CENPA, CFH, CHDH, CHIT1, CKAP2L, CLEC4C, CLEC4F, CLNK, COL17A1, CRISP2, CRISP3, CTSE, CTSG, CYP19A1, CYR1, DEFA4, DENND2C, DEPDC1, DGKK, DLC1, DLGAP5, DNAH10, DOC2B, DSP, ELANE, ERG, FAM20A, FAM83A, FBN1, FFAR3, G0S2, GGT5, GLB1L2, GJB6, GPR84, GRAMD1C, GYPA, HBM, HMGB3, HP, HPGD, HRK, IGLL1, IL1R2, IL1RL1, INHBA, IQGAP3, ITGA7, ITGB4, KIF15, KIF20A, KLF14, LAMB3, LCN2, LGR4, LPL, LTF, MAFG, MERTK, METTL7B, MMP8, MMP9, MPO, MRC1, MROCK1, MS4A3, MS4A4A, NECAB1, NEIL3, NEK2, NRXN2, NUF2, OLAH, OLFM4, OLIG2, PCOLCE2, PCSK9, PHF24, PIGR, PLAAT2, PPARG, PRTN3, PTGES, PYCR1, RAB3IL1, RASGRF1, RETN, RHCE, RIPOR3, RPGRIP1, RRM2, S100A12, S100A8, SCN8A, SEMA6B, SERPINB10, SIGLEC8, SIL1, SLC16A1, SLC28A3, SLC39A8, SLC4A10, SLC51A, SLC6A19, SLC8A3, SLCO4A1, SMIM1, SMPDL3A, SPATC1, SPOP, SSBP2, TCN1, TCTEX1D1, TDRD9, TEAD2, TFRC, THBS1, TIMP3, TLN2, TMEM255A, TMEM45A, TNFAIP8L3, TNIP3, TROAP, TTK, VSIG4, WNT3, YPEL4, and ZDHHC19.

23. The method of claim 22, wherein the plurality of genes comprises CCL4L2, GPR84, HRK, MMP8, GGT5, and RASGRF1.
24. The method of claim 22, wherein the plurality of genes is CCL4L2, GPR84, HRK, MMP8, GGT5, and RASGRF1.
25. The method of any one of claims 1 to 24, wherein determining the level of expression comprises detecting nucleic acids encoded by each of the plurality of genes.
26. The method of claim 25, wherein determining the level of expression comprises one or more of a polymerase chain reaction (PCR) amplification method, a non-PCR based

amplification method, reverse transcriptase-(RT) PCR, Q-beta replicase amplification, ligase chain reaction, signal amplification (Ampliprobe), light cycling, differential display, Northern analysis, hybridization, microarray analysis, DNA sequencing, RNA sequencing (RNA-Seq), MassArray analysis and MALDI-TOF mass spectrometry.

27. The method of claim 26, wherein determining the level of expression comprises a polymerase chain reaction (PCR) amplification method.
28. The method of any one of claims 25 to 27, wherein determining the level of expression comprises RNA sequencing (RNA-Seq).
29. The method according to any one of claims 1 to 28, wherein the biological sample comprises sputum, blood, nasal brushings, throat swabs, urine, amniotic fluid, plasma, serum, saliva, semen, bone marrow, tissue or fine needle biopsy samples, stool, bronchoalveolar lavage fluid, cerebrospinal fluid, peritoneal fluid, pleural fluid, skin, or cells therefrom.
30. The method according to any one of claims 1 to 28, wherein the biological sample comprises blood.
31. The method according to any one of claims 1 to 30, wherein the biological sample has been obtained from the subject prior to admission in an intensive care unit.
32. The method according to any one of claims 1 to 30, wherein the biological sample has been obtained from the subject at first clinical presentation.
33. The method according to any one of claims 1 to 30, wherein the biological sample has been obtained from the subject within the first day after entry into an intensive care unit.
34. A use of one or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype, for treatment of sepsis in a subject classified as having the sepsis mechanistic endotype by a method as defined in any one of claims 1 to 21 and 25 to 33, as dependent on any one of claims 1 to 21.

35. One or more therapies that act specifically against a mechanism associated with a sepsis mechanistic endotype for use to treat sepsis in a subject classified as having the sepsis mechanistic endotype by a method as defined in any one of claims 1 to 21 and 25 to 33, as dependent on any one of claims 1 to 21.
36. A use of an effective amount of one or more antibiotics for treatment of sepsis in a subject predicted as having high or intermediate severity sepsis by a method as defined in any one of claims 22 to 24 and claims 25 to 33, as dependent on any one of claims 22 to 24.
37. The use of claim 36, wherein the one or more antibiotics is one or a combination of a glycopeptide, a cephalosporin, a beta-lactam, a beta-lactamase inhibitor, a carbapenem, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide and a monobactam.
38. One or more antibiotics for use to treat sepsis in a subject predicted as having high or intermediate severity sepsis by a method as defined in any one of claims 22 to 24 and claims 25 to 33, as dependent on any one of claims 22 to 24.
39. The one or more antibiotics for the use of claim 38, wherein the one or more antibiotics is one or a combination of a glycopeptide, a cephalosporin, a beta-lactam, a beta-lactamase inhibitor, a carbapenem, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide and a monobactam.
40. A kit:
(a) for classifying a subject into a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the kit comprising gene specific reagents, each of the gene specific reagents capable of detecting an expression product of:
(i) a respective one of a plurality of genes or complement thereof in an NPS endotype sub-signature, an INF endotype sub-signature, an IHD endotype sub-signature, an IFN endotype sub-signature, an ADA endotype sub-signature or combinations thereof, wherein the NPS endotype sub-signature, the INF endotype sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, the ADA endotype sub-signature or combinations thereof are as defined in any one of claims 1 and 4 to 13; or

(ii) a respective one of a plurality of genes or complement thereof in an NPS endotype signature pair, an INF endotype signature pair, an IHD endotype signature pair, an IFN endotype signature pair, an ADA endotype signature pair or combinations thereof, wherein the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, the ADA endotype signature pair or combinations thereof are as defined in any one of claims 14 and 16 to 21; or

(b) for predicting severity of sepsis in a subject, wherein the severity of the sepsis is selected from high severity sepsis, intermediate severity sepsis and low severity sepsis, wherein high severity sepsis means a sequential organ failure assessment (SOFA) score of greater than or equal to 5, intermediate severity sepsis means a SOFA score of greater than or equal to 2 but less than 5, and low severity sepsis means a SOFA score of less than 2, the kit comprising gene specific reagents, each of the gene specific reagents capable of detecting an expression product of a respective one of a plurality of genes as defined in any one of claims 22 to 24 or complement thereof; and optionally instructions for use.

41. A method for identifying a candidate agent for the treatment of sepsis in a subject classified as having a sepsis mechanistic endotype selected from neutrophilic-suppressive (NPS), inflammatory (INF), innate host defense (IHD), interferon (IFN) and adaptive (ADA) endotypes, the method comprising: (a) contacting a cell having the sepsis endotype with a test agent, (b) determining the level of expression for each of a plurality of genes in the cell to provide an expression signature; (c) comparing the expression signature with a reference signature, wherein the reference signature represents the level of expression of the plurality of genes in a normal cell; and (d) selecting the test agent as a candidate agent for treatment of the sepsis when the expression signature substantially corresponds with the reference signature, wherein the expression signature and reference signature comprise:
 - (a) an NPS endotype sub-signature for an NPS endotype cell, an INF endotype sub-signature for an INF endotype cell, an IHD endotype sub-signature for an IHD endotype cell, an IFN endotype sub-signature for an IFN endotype cell and an ADA endotype sub-signature for an ADA endotype cell, wherein the NPS endotype sub-signature, the INF endotype sub-signature, the IHD endotype sub-signature, the IFN endotype sub-signature, the ADA endotype sub-signature or combinations thereof are as defined in any one of claims 1 and 4 to 13; or

(b) an NPS endotype signature pair for an NPS endotype cell, an INF endotype signature pair for an INF endotype cell, an IHD endotype signature pair for an IHD endotype cell, an IFN endotype signature pair for an IFN endotype cell, and an ADA endotype signature pair for an ADA endotype cell, wherein the NPS endotype signature pair, the INF endotype signature pair, the IHD endotype signature pair, the IFN endotype signature pair, the ADA endotype signature pair or combinations thereof are as defined in any one of claims 14 and 16 to 21.

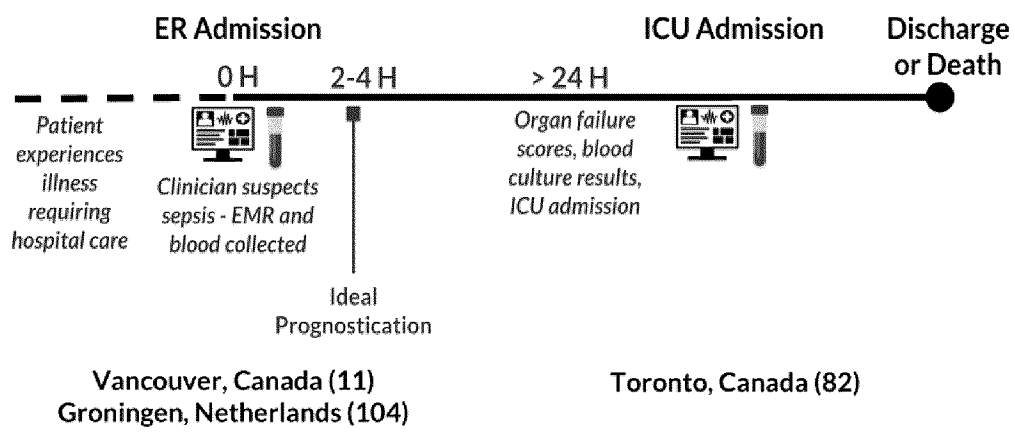


FIG. 1

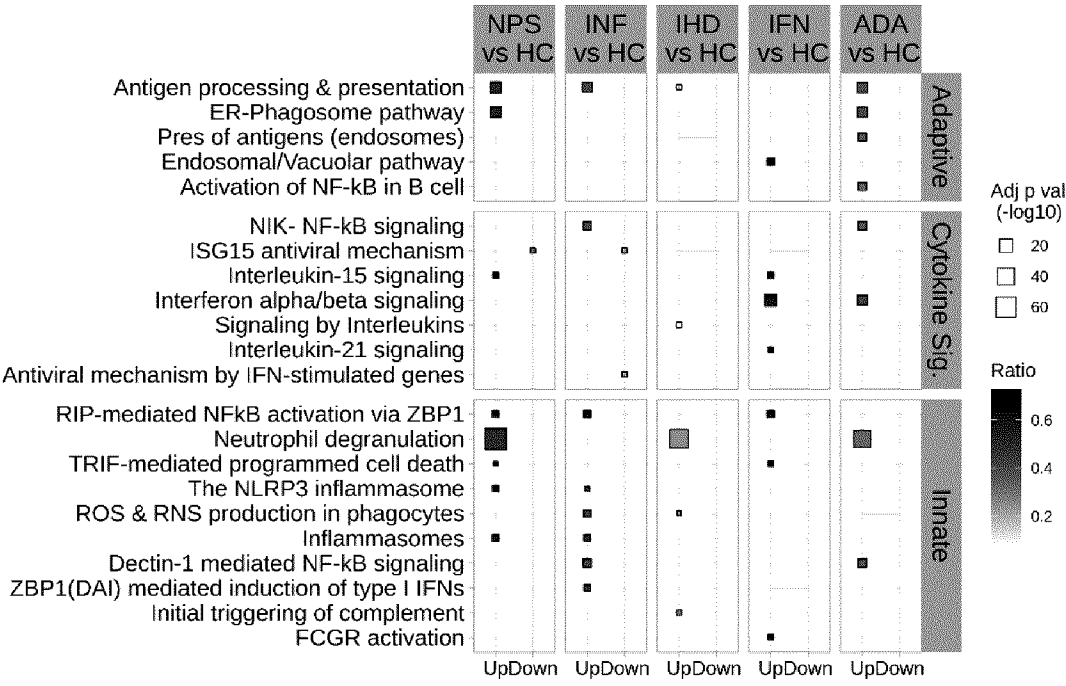


FIG. 2

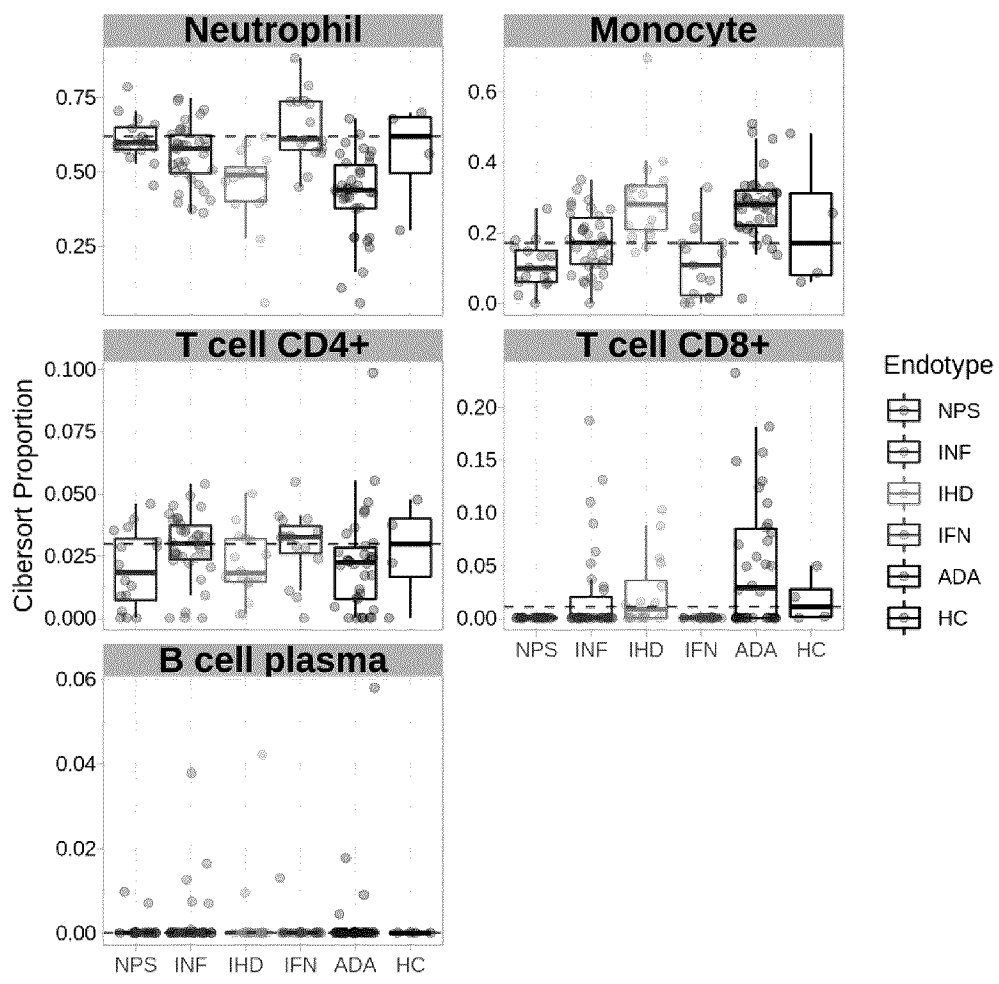


FIG. 3

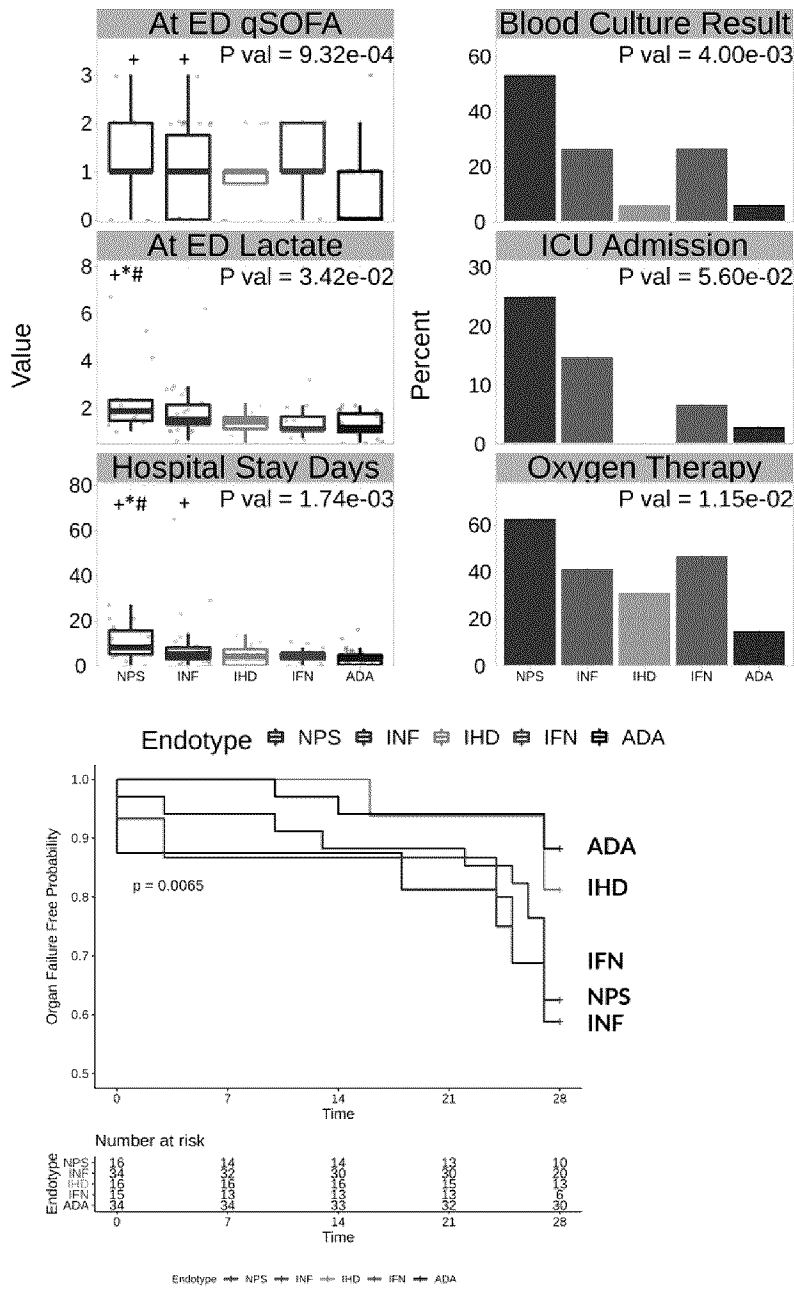
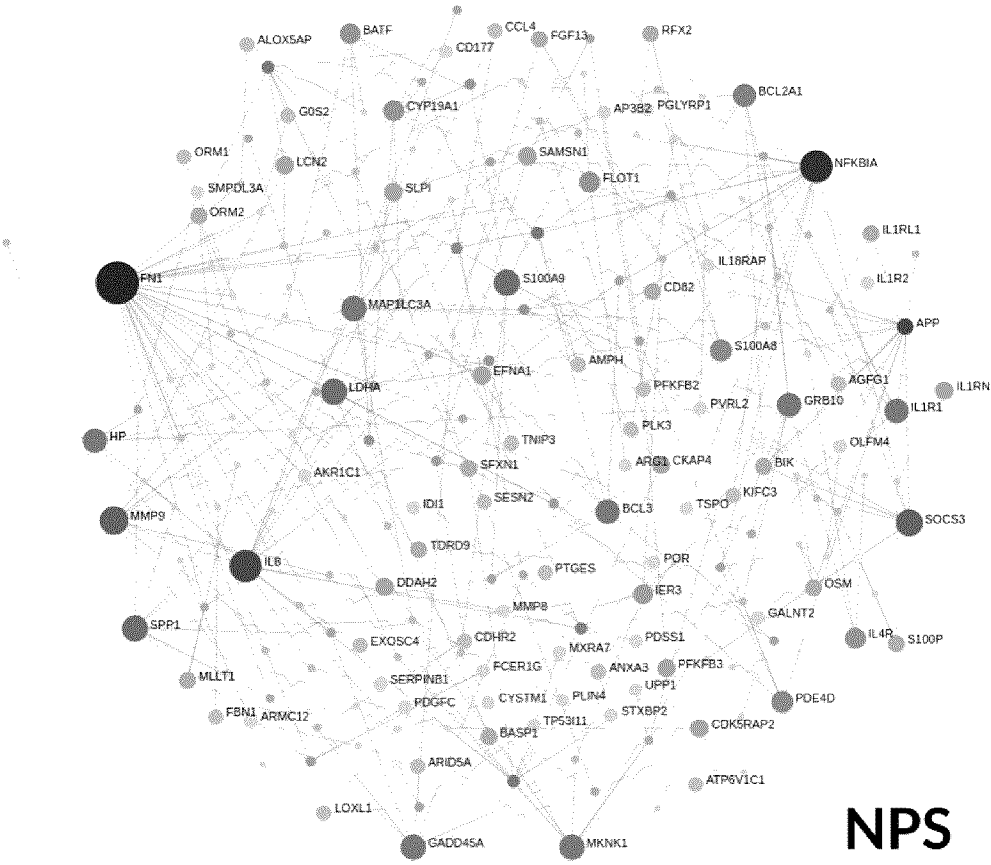
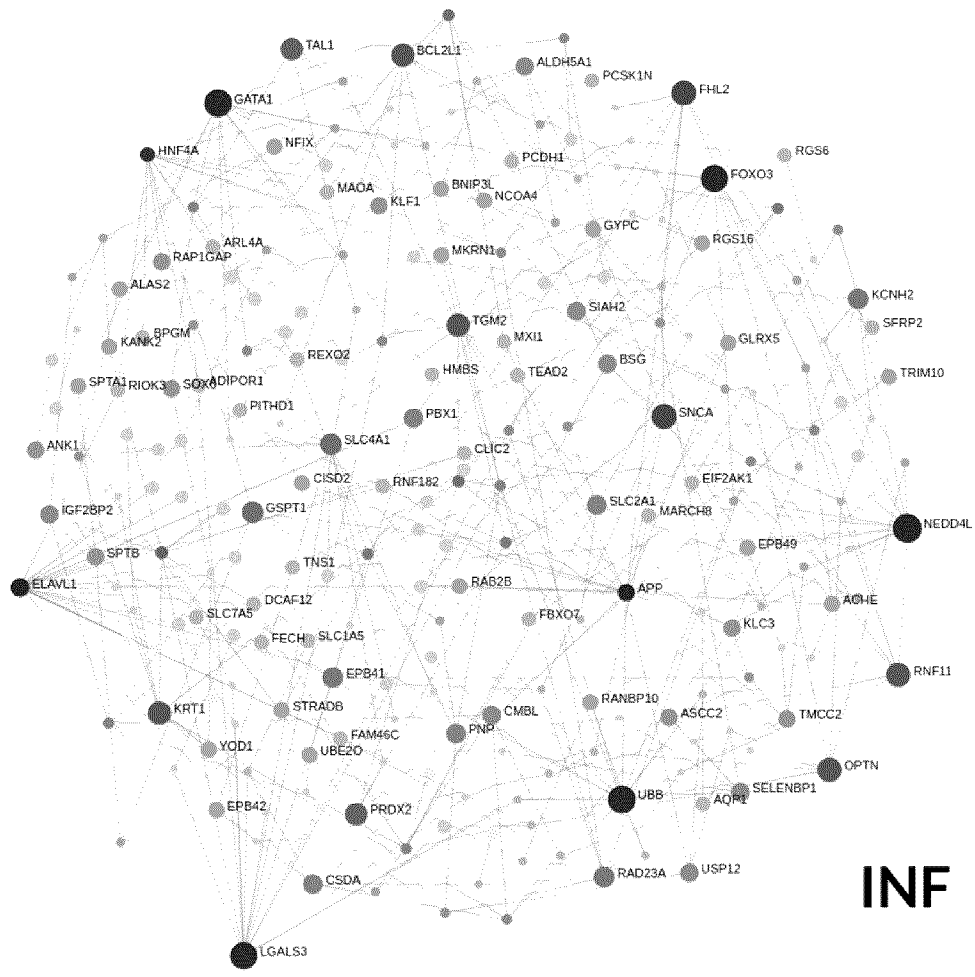


FIG. 4



NPS

FIG. 5



INF

FIG. 6

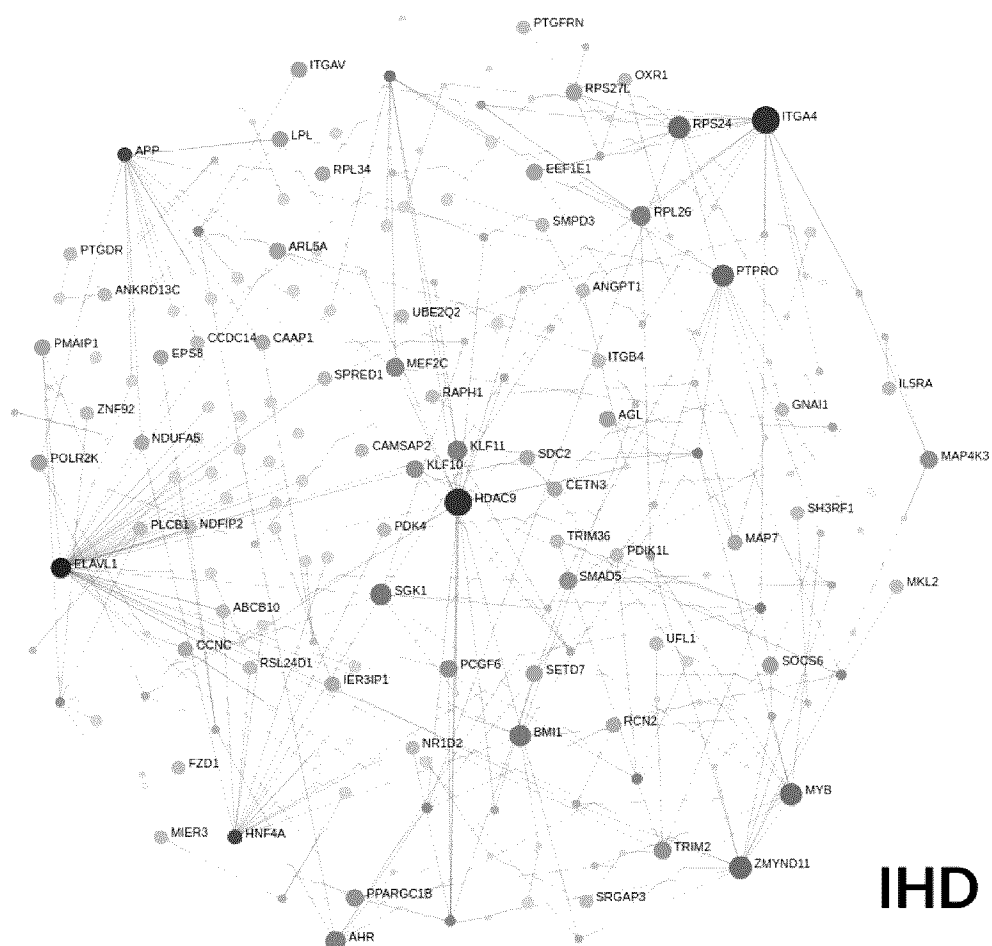


FIG. 7

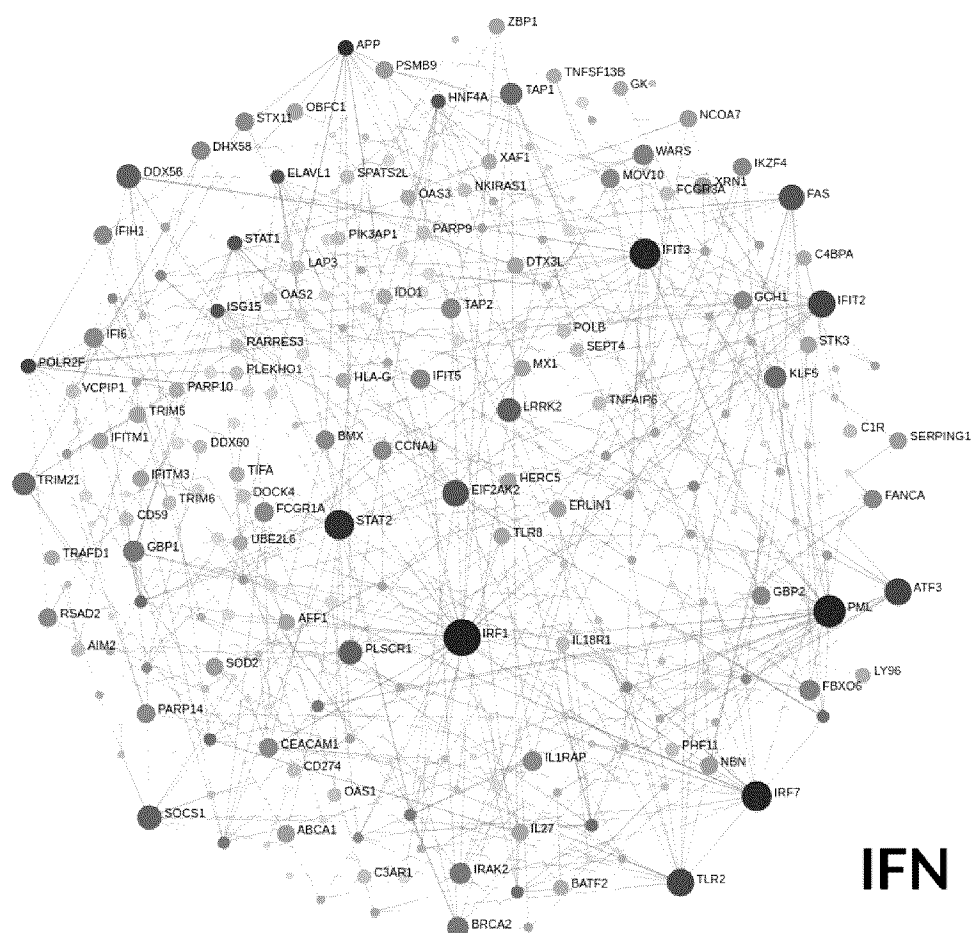


FIG. 8

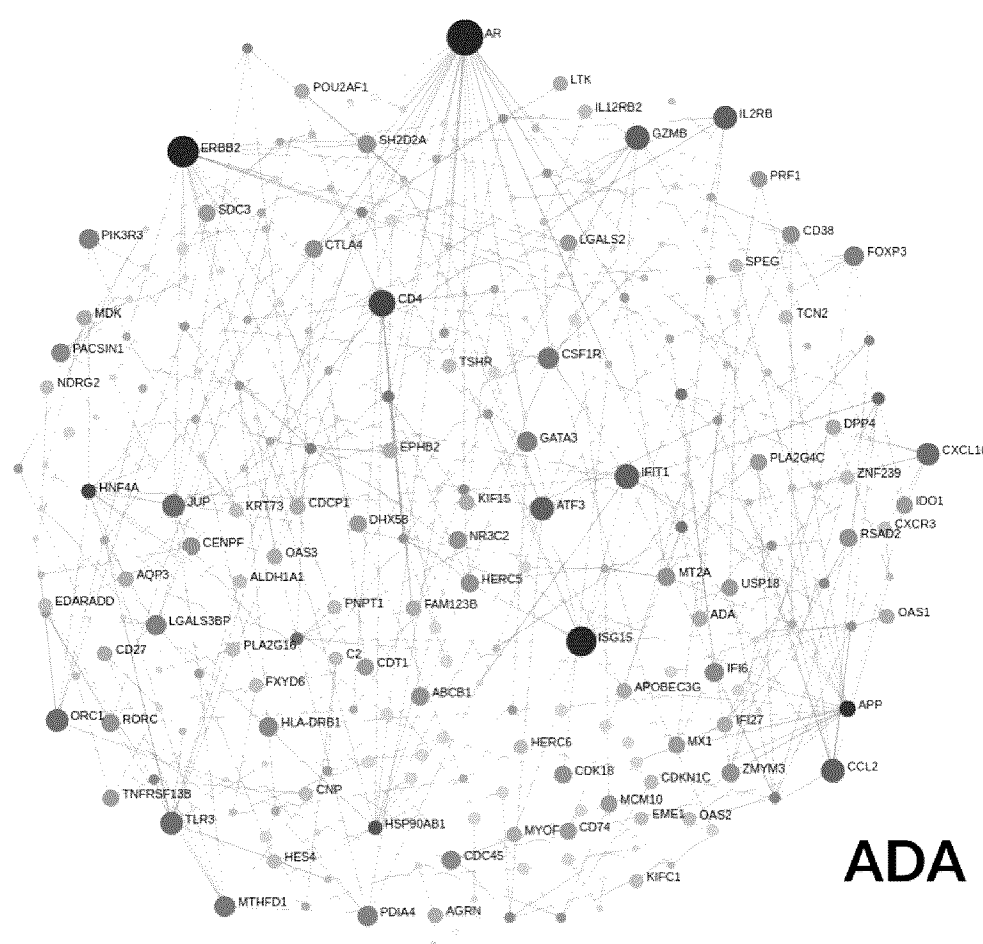


FIG. 9

9/15

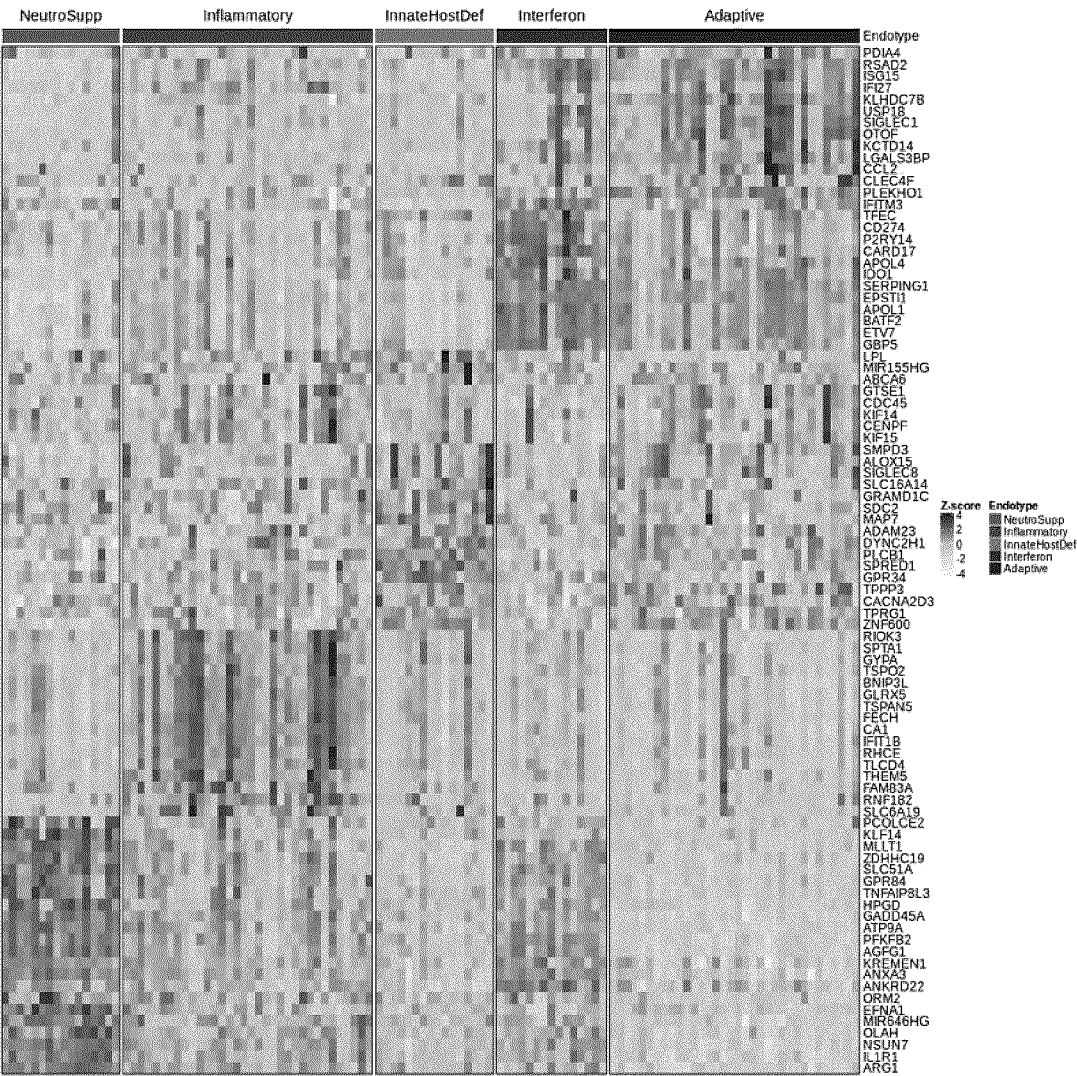


FIG. 10

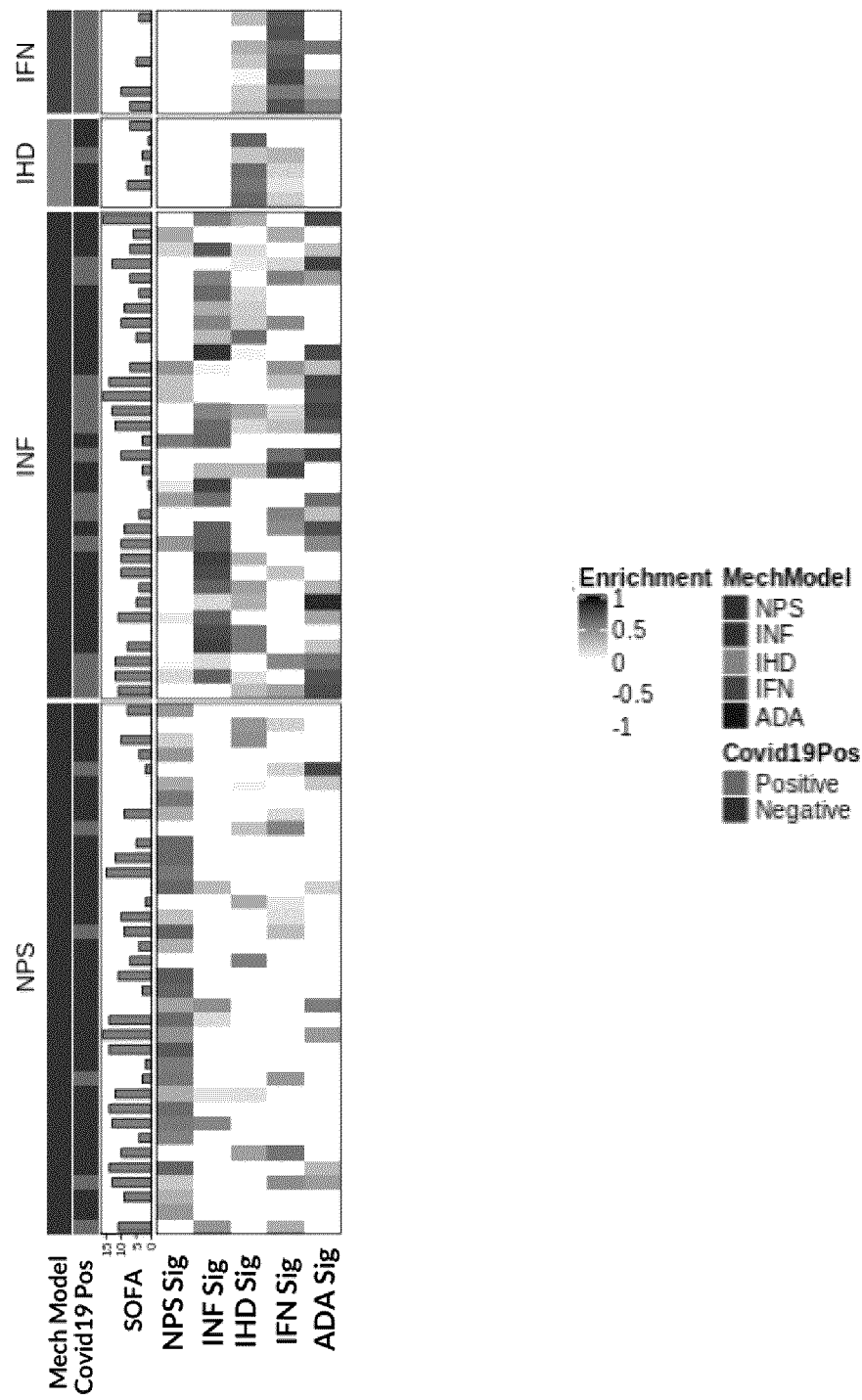


FIG. 11

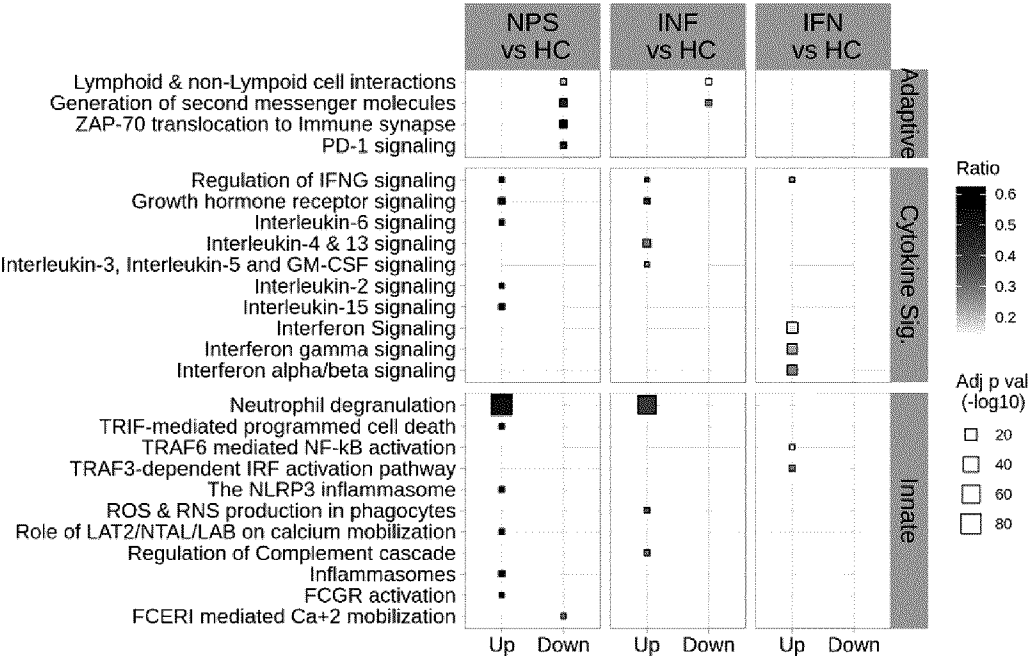


FIG. 12

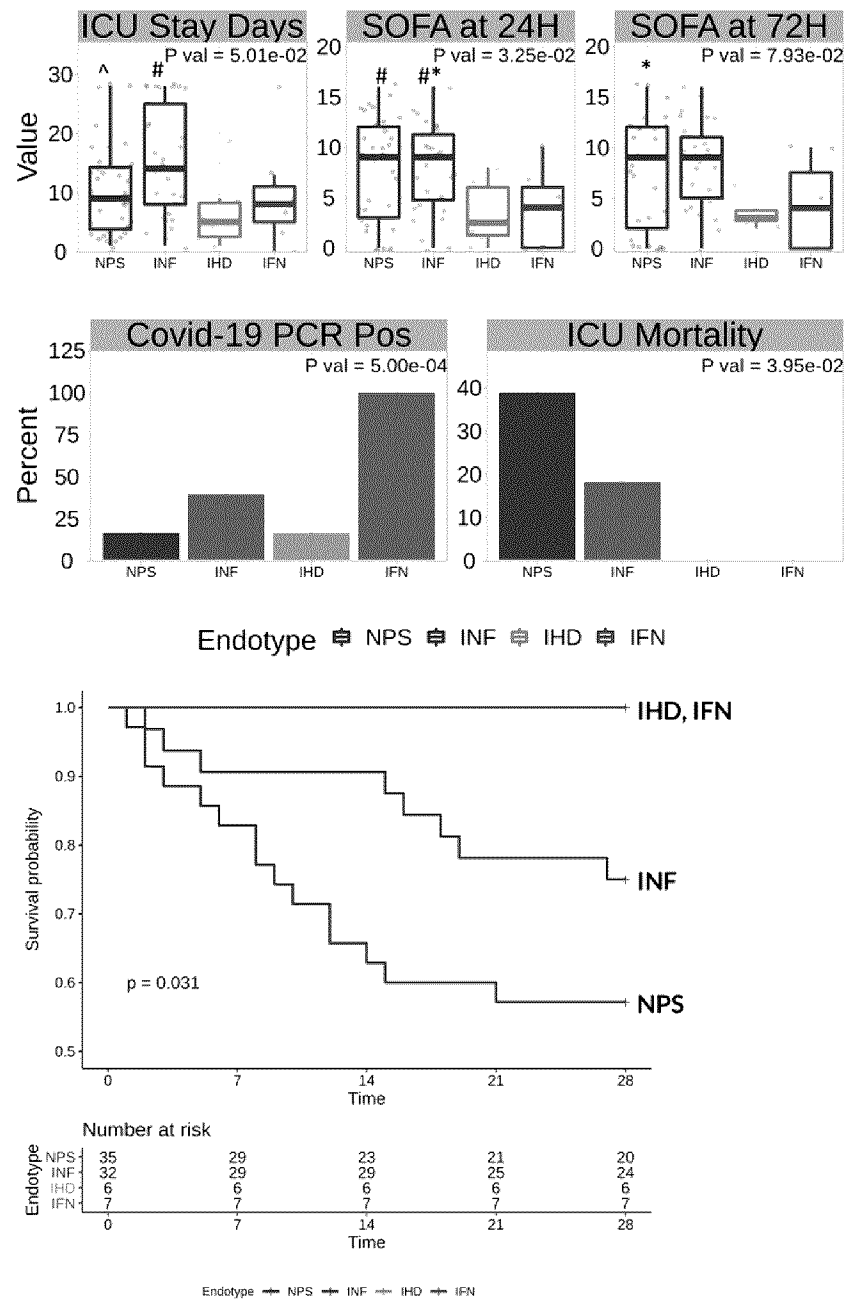


FIG. 13

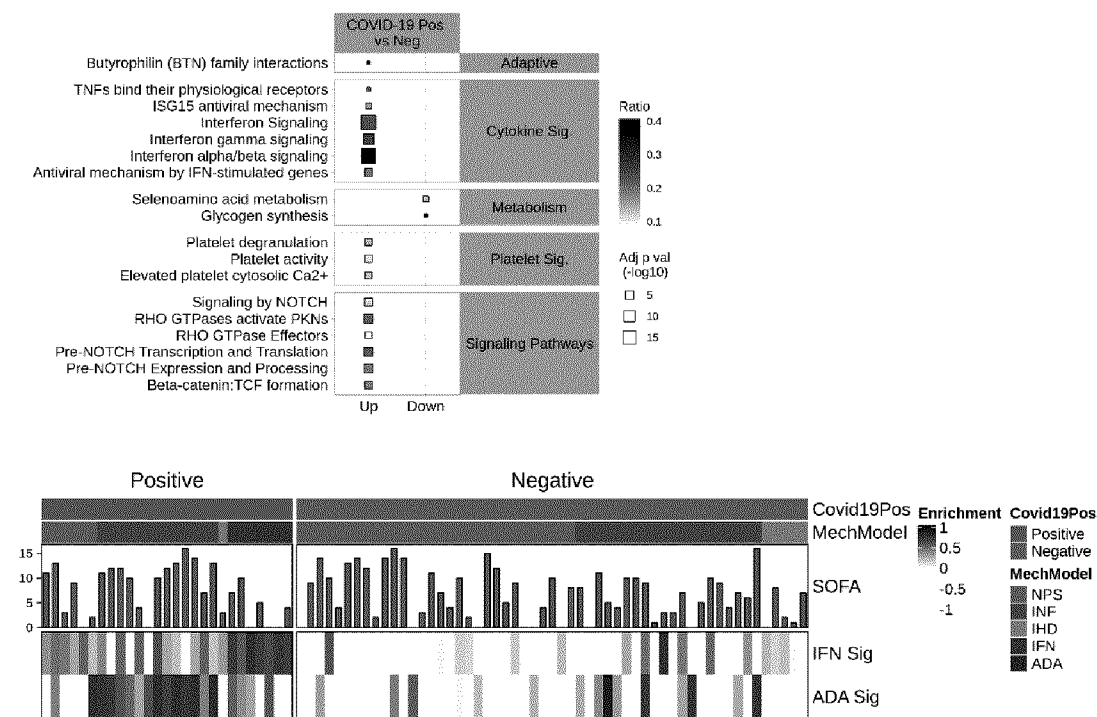


FIG. 14

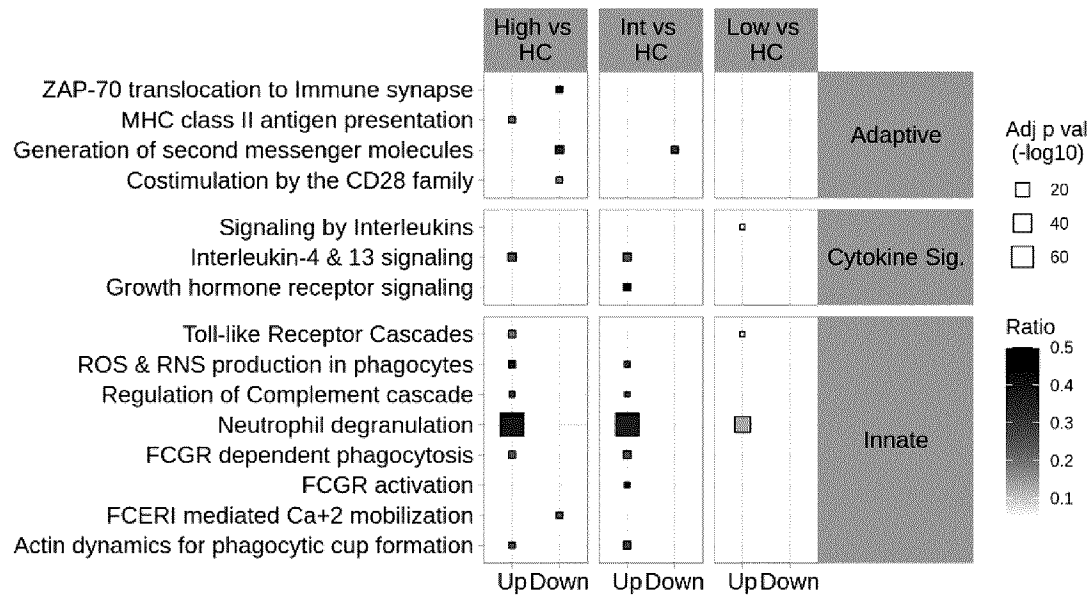


FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2022/050831

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C12Q 1/6809** (2018.01), **C12Q 1/6883** (2018.01), **G01N 33/50** (2006.01), **G16B 25/10** (2019.01), **A61P 31/04** (2006.01)

CPC: C12Q 1/6809 (2020.01), C12Q 1/6883 (2020.01), G01N 33/50 (2020.01), G16B 25/10 (2020.01), A61P 31/04 (2020.01), C12Q 2539/00 (2020.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C12Q 1/6809 (2018.01), C12Q 1/6883 (2018.01), G01N 33/50 (2006.01), G16B 25/10 (2019.01), A61P 31/04 (2006.01)
CPC: C12Q 1/6809 (2020.01), C12Q 1/6883 (2020.01), G01N 33/50 (2020.01), G16B 25/10 (2020.01), A61P 31/04 (2020.01), C12Q 2539/00 (2020.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Questel Orbit, CaPlus, Pubmed, SCOPUS, STM Source, Google Scholar

Keywords: sepsis, ARG1, AGFG1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	BAGHELA, A. <i>et al.</i> Predicting sepsis severity at first clinical presentation: The role of endotypes and mechanistic signatures. <i>eBioMedicine</i> 75: 103776 (10-01-2022) doi: 10.1016/j.ebiom.2021.103776 *whole document*	1-4, 14-16, 25-35, and 40-41
Y	MASLOVE, D. <i>et al.</i> Identification of sepsis subtypes in critically ill adults using gene expression profiling. <i>Critical Care</i> 16:R183 and Supplementary Materials (04-10-2012) doi: 10.1186/cc11667 *whole document and Additional file 3: "Sepsis subtype gene signature"; cited by applicant*	1-4, 14-16, 25-35, and 40-41

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

* "A" "D" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance document cited by the applicant in the international application earlier application or patent but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search
26 July 2022 (26-07-2022)Date of mailing of the international search report
09 August 2022 (09-08-2022)Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 819-953-2476

Authorized officer

Christopher Hill (819) 921-3296

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2022/050831

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SWEENEY, T. et al. Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. Critical Care Medicine 46(6):915-925 and Supplemental Digital Content (30-06-2018) doi:10.1097/CCM.0000000000003084 *whole document and Supplemental Table 6 in Supplementary Digital content; cited by applicant*	1-4, 14-16, 25-35, and 40-41
Y	MAMOOD, S. A sepsis gene expression signature in the whole blood. OSF Preprints (20-07-2020) doi:10.31219/osf.io/fbdwe *whole document, particularly Fig. 2 and Table 1*	1-4, 14-16, 25-35, and 40-41
A	SCICLUNA, B. et al. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. Lancet Respiratory Medicine 5(10):816-826 (29-08-2017)	-
A	US2017/0191129A1 (BRANDON et al.) 06 July 2017 (06-07-2017)	-
A	WO2020/096984A1 (LEE et al.) 14 May 2020 (14-05-2020)	-

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2022/050831**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

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

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

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

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

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

This International Searching Authority found multiple inventions in this international application, as follows:

See two (2) extra sheets

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

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

Claims 1-4, 14-16, 25-35, and 40-41; specifically those embodiments of these claims which feature the plurality of genes consisting of the pair AGFG1/ARG1

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CA2022/050831

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2017191129A1	06 July 2017 (06-07-2017)	US11047010B2 AU2015213486A1 AU2015213486A9 AU2015213486B2 CA2930925A1 CN105981026A DK3103046T3 EP3103046A1 EP3103046A4 EP3103046B1 JP2017512304A US2015259746A1 US10865447B2 US2015218640A1 WO2015117204A1 WO2015117204A9	29 June 2021 (29-06-2021) 02 June 2016 (02-06-2016) 07 July 2016 (07-07-2016) 22 October 2020 (22-10-2020) 13 August 2015 (13-08-2015) 28 September 2016 (28-09-2016) 02 June 2020 (02-06-2020) 14 December 2016 (14-12-2016) 23 August 2017 (23-08-2017) 25 March 2020 (25-03-2020) 18 May 2017 (18-05-2017) 17 September 2015 (17-09-2015) 15 December 2020 (15-12-2020) 06 August 2015 (06-08-2015) 13 August 2015 (13-08-2015) 23 June 2016 (23-06-2016)
WO2020096984A1	14 May 2020 (14-05-2020)	US2021388443A1	16 December 2021 (16-12-2021)

Continuation of Box III, "Observations where unity of invention is lacking" (1st of 2 extra sheets continuing Box III)

The claims are directed to a plurality of inventive concepts as follows:

Group A+: Claims 4-5 and 17 (all wholly) and claims 1-3, 14-16, 25-35, and 40-41 (all partially) are directed to methods for classifying a subject into the neutrophilic-suppressive (NPS) endotype of sepsis and uses, therapies, and kits related thereto. For reasons to be detailed below, Group A+ comprises 9.9×10^{27} possible separate inventions depending upon how many and which of at least two of 93 relevant genes recited in claim 1 are selected for use in the methods, uses, therapies, and kits.

Group B+: Claims 6-7 and 18 (all wholly) and claims 1-3, 14-16, 25-35, and 40-41 (all partially) are directed to methods for classifying a subject into the inflammatory (INF) endotype of sepsis and uses, therapies, and kits related thereto. For reasons to be detailed below, Group B+ comprises 4.4×10^{40} possible separate inventions depending upon how many and which of at least two of 135 relevant genes recited in claim 1 are selected for use in the methods, uses, therapies, and kits.

Group C+: Claims 8-9 and 19 (all wholly) and claims 1-3, 14-16, 25-35, and 40-41 (all partially) are directed to methods for classifying a subject into the innate host defense (IHD) endotype of sepsis and uses, therapies, and kits related thereto. For reasons to be detailed below, Group C+ comprises 1.1×10^9 possible separate inventions depending upon how many and which of at least two of 30 relevant genes recited in claim 1 are selected for use in the methods, uses, therapies, and kits.

Group D+: Claims 10-11 and 20 (all wholly) and claims 1-3, 14-16, 25-35, and 40-41 (all partially) are directed to methods for classifying a subject into the interferon (IFN) endotype of sepsis and uses, therapies, and kits related thereto. For reasons to be detailed below, Group D+ comprises 4.2×10^6 possible separate inventions depending upon how many and which of at least two of 22 relevant genes recited in claim 1 are selected for use in the methods, uses, therapies, and kits.

Group E+: Claims 12-13 and 21 (all wholly) and claims 1-3, 14-16, 25-35, and 40-41 (all partially) are directed to methods for classifying a subject into the adaptive (ADA) endotype of sepsis and uses, therapies, and kits related thereto. For reasons to be detailed below, Group E+ comprises 8.8×10^{12} possible separate inventions depending upon how many and which of at least two of 43 relevant genes recited in claim 1 are selected for use in the methods, uses, therapies, and kits.

Group F+: Claims 22-24 and 36-39 (all wholly) and claims 25-33 and 40 (all partially) are directed to methods for predicting severity of sepsis in a subject and uses of antibiotics, antibiotics for use, and kits related thereto. For reasons to be detailed below, Group F+ comprises 1.8×10^{47} possible separate inventions depending upon how many and which of at least two of 157 relevant genes recited in claim 22 are selected for use in the methods, uses, therapies, and kits.

The inventions of Groups A+, B+, C+, D+, E+ and F+ share the feature of determining, in a biological sample from the subject, a level of expression for each of a plurality of genes to produce a gene signature useful in the classification of sepsis. Groups A+, B+, C+, D+, and E+ are directed to determining gene signatures for different endotypes of sepsis while Group F+ is directed towards determining gene signatures for severity of sepsis. With respect to the classification of endotypes, there is no overlap between the lists of the 93 genes recited in claim 1 as being relevant to Group A+, the 135 genes recited in claim 1 as being relevant to Group B+, the 30 genes recited in claim 1 as being relevant to Group C+, the 22 genes recited in claim 1 as being relevant to Group D+, and the 43 genes recited in claim 1 as being relevant to Group E+. Some, but not all, of the 157 genes recited in claim 22 as being relevant to classification of sepsis severity (Group F+) are also in the lists of genes in claim 1 recited as being relevant to sepsis endotype.

First, as Groups A+ through E+ are directed to determining sepsis endotype and Group F+ is directed to determining sepsis severity, Group F+ lacks unity with any other group *a priori*.

Second, determining sepsis endotype by identifying endotype 'signatures' in gene expression data was known from multiple disclosures in the prior art. As but one example, Maslove *et al.* (*Critical Care* 2012, 16:5, R183), disclosed that sepsis subtypes can be identified based on different gene expression patterns ("Conclusions", pg. 9 of 11). Three of the genes identified by Maslove *et al.* in their "Sepsis subtype gene signature" ("Additional File 3" of Maslove *et al.*) overlap with genes recited in the instant application, including ARG1 and ANXA.

Therefore, methods employing gene signatures produced by determining the level of expression of a plurality of genes (wherein a plurality is at least two, per paragraph [0066] of the instant application) to classify sepsis was known in the art and at least some pluralities of the recited genes had previously been disclosed as being useful in such methods. Groups A+ through F+ therefore lack unity with each other *a posteriori*, particularly in light of the absence of overlap in the list of genes recited as being relevant to each sepsis endotype.

Further, given the prior disclosure in Maslove *et al.* of at least one of the recited pairs of genes disclosed in the instant application as being useful in sepsis classification (ARG1/ANXA; see paragraph [00139] of the instant application), each of the possible pluralities within Groups A+ through F+ represent numerous separate inventions. A plurality of genes may be two genes, three genes, four genes, and so on up to the maximum number of genes recited as being relevant to each of Groups A+ through F+. For example, a plurality of genes selected from the list relevant to Group A+ could be two genes (4278 possible combinations), three genes (632710 possible combinations), four genes (24,359,335 possible combinations), and so on all the way to 93 genes (1 possible combination) selected from the 93 genes recited as relevant to the NPS endotype in claim 1. Calculation of all possible gene combinations in all possible sizes of pluralities of genes for each of Groups A+ through F+ produces a grand total of 1.83×10^{47} possible inventions.

Continued on extra sheet, immediately following

Further continuation of Box III, "Observations where unity of invention is lacking" (2nd of 2 extra sheets continuing Box III)

The first invention of the application will be searched. The first invention is considered to be defined by the smallest possible plurality of genes, in this case a pair, produced by selecting the first two genes recited in the first Group of inventions.

Therefore, **the separate invention of Group A+ further defined by determining the level of expression of a plurality (in this case, a pair) of genes consisting of AGFG1 and ARG1 will be searched.** It is noted that this plurality of genes is expressly recited in claim 14, which recites pairs of genes useful in determining sepsis endotype. It is further noted that the plurality to be examined does not correspond to the plurality of 21 genes in claim 5 and that the AGFG1/ARG1 pair is also not within the scope of claim 17, despite claims 5 and 17 being part of broader Group A+. Therefore the **embodiments of claims 1-4, 14-16, 25-35, and 40-41 featuring the plurality of genes consisting of the pair AGFG1/ARG1 will be searched.**