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(54) Title: METHODS FOR DIAGNOSIS OF BACTERIAL AND VIRAL INFECTIONS

(57) Abstract: Methods for diagnosis of bacterial and viral infections are disclosed. In particular, the invention relates to the use of biomarkers that can determine whether a patient with acute inflammation has a bacterial or viral infection.

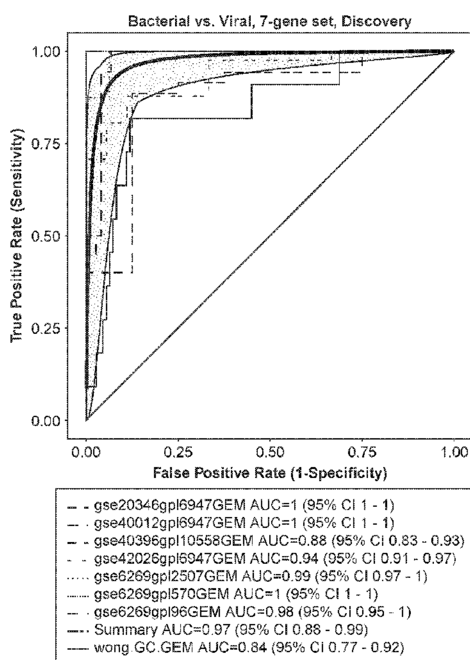

FIG. 1A

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METHODS FOR DIAGNOSIS OF BACTERIAL AND VIRAL INFECTIONS

CROSS-REFERENCING

5 This application claims the benefit of U.S. provisional application serial no. 62/346,962, filed on June 7, 2016, which application is incorporated by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with Government support under contracts AI109662 and 10 AI057229 awarded by the National Institutes of Health. The Government has certain rights in the invention.

TECHNICAL FIELD

The present invention pertains generally to methods for diagnosis of bacterial and 15 viral infections. In particular, the invention relates to the use of biomarkers that can distinguish whether a patient with acute inflammation has a bacterial or viral infection.

BACKGROUND

Early and accurate diagnosis of infection is key to improving patient outcomes 20 and reducing antibiotic resistance. The mortality rate of bacterial sepsis increases 8% for each hour by which antibiotics are delayed[1]; however, giving antibiotics to patients without bacterial infections increases rates of morbidity and antimicrobial resistance. The rate of inappropriate antibiotic prescriptions in the hospital setting is estimated at 30-50%, and would be aided by improved diagnostics[2,3]. Strikingly, close to 95% of patients 25 given antibiotics for suspected enteric fever have negative cultures[4]. There is currently no gold-standard point of care diagnostic that can broadly determine the presence and type of infection. Thus, the White House has established a National Action Plan for Combating Antibiotic-Resistant Bacteria, which called for "point-of-need diagnostic tests to distinguish rapidly between bacterial and viral infections"[5].

30 While new PCR-based molecular diagnostics can profile pathogens directly from a blood culture[6], such methods rely on the presence of adequate numbers of pathogens in

the blood. Moreover, they are limited to detecting a discrete range of pathogens. As a result, there is growing interest in molecular diagnostics that profile the host gene response. These include diagnostics that can distinguish the presence of infection as compared to inflamed but non-infected patients, such as our 11-gene 'Sepsis MetaScore'[7]
5 (SMS) (which has been validated across multiple cohorts[8]) among others[9,10]. Other groups have focused on gene sets that can distinguish between types of infections, such as bacterial versus viral infections[11-13]. Tsalik et al. described a model that distinguishes among all three classes (i.e., non-infected patients and those with bacterial or viral illness), though this model required the measurement of 122 probes[14]. We also previously
10 described a 'Meta-Virus Signature' that describes a common response to viral infection, but contained too many genes (396) for clinical application[15]. Overall, while great promise has been shown in this field, no host gene expression infection diagnostic has yet made it into clinical practice.

The data from these biomarker studies and dozens of other genome-wide
15 expression studies in sepsis and acute infections have been published and deposited for further study in public databases such as NIH Gene Expression Omnibus (GEO) and EBI ArrayExpress. These data are a largely untapped resource that can be used for both biomarker discovery and validation. We have previously shown that our integrated multi-cohort analysis of gene expression produces robust diagnostic tools for sepsis[7], specific
20 types of viral infections[15], and active tuberculosis[16]. Further, these data are also useful as a benchmarking and validation tool for novel host gene expression diagnostics[17]. However, such validation in public data has previously been limited to only those cohorts which contain at least two classes of interest (i.e., in which a direct comparison between classes is possible), since inter-study technical differences preclude direct comparison of
25 diagnostic scores between cohorts.

There remains a need for sensitive and specific diagnostic tests that can distinguish between bacterial and viral infections.

SUMMARY

30 The invention relates to the use of biomarkers that can determine whether a patient with acute inflammation has a bacterial or viral infection. These biomarkers can

be used alone or in combination with one or more additional biomarkers or relevant clinical parameters in prognosis, diagnosis, or monitoring treatment of an infection.

In one embodiment, the invention is drawn to a method of developing a classification used for diagnosing an infection in a patient, the method including: (a) measuring levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers include at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers include at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB; (b) using the levels of expression of the biomarkers to develop a classification or generative algorithm which can determine presence or probability of bacterial or viral infection in the patient; and (c) applying the algorithm to diagnose the patient as having or as likely to have bacterial or viral infection.

In one embodiment, the invention is drawn to a method for diagnosis of an infection in a patient, the method including analyzing levels of expression of at least two genes, wherein the at least two genes are predictive of either a viral or bacterial infection; and wherein the levels of expression of the at least two genes provide an area under a curve for predicting a viral or bacterial infection of at least 0.80; and diagnosing the patient as having either a bacterial or viral infection.

In one embodiment, the invention is drawn to a method for diagnosing and treating an infection in a patient, the method including (a) obtaining a biological sample from the patient; (b) measuring the levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB biomarkers in the biological sample; (c) analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for

the biomarkers, wherein increased levels of expression of the IFI27, JUP, LAX1 biomarkers compared to the reference value ranges for the biomarkers for a control subject indicate that the patient has a viral infection, and increased levels of expression of the HK3, TNIP1, GPAA1, CTSB biomarkers compared to the reference value ranges for the biomarkers for a control subject indicate that the patient has a bacterial infection; and (d) administering an effective amount of an anti-viral agent to the patient if the patient is diagnosed with a viral infection or administering an effective amount of an antibiotic to the patient if the patient is diagnosed with a bacterial infection.

In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

In any embodiment, the levels of the biomarkers can be compared to time-matched reference values for infected or non-infected subjects.

In any embodiment, the method can include calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

In any embodiment, the method can include normalizing data using COCONUT normalization.

In any embodiment, the patient can be a human being.

In any embodiment, measuring the level of the plurality of biomarkers can include performing microarray analysis, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), a Northern blot, or a serial analysis of gene expression (SAGE).

In one embodiment, the invention is drawn to a method of diagnosing and treating a patient having inflammation, the method including (a) obtaining a biological sample from the patient; (b) measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in the biological sample; (c) first analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, wherein increased levels of expression of the

CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection; (d) further analyzing the levels of expression of the IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB biomarkers, if the patient is diagnosed as having an infection, wherein increased levels of expression of the IFI27, JUP, LAX1 biomarkers compared to reference value ranges for the biomarkers for a control subject indicate that the patient has a viral infection, and increased levels of expression of the HK3, TNIP1, GPAA1, CTSB biomarkers compared to the reference value ranges for the biomarkers for the control subject indicate that the patient has a bacterial infection; and (e) administering an effective amount of an anti-viral agent to the patient if the patient is diagnosed with a viral infection, or administering an effective amount of an antibiotic to the patient if the patient is diagnosed with a bacterial infection.

In any embodiment, the method can include calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition.

In any embodiment, the method can include calculating a bacterial/viral metascore for the patient if the patient is diagnosed as having an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

In any embodiment, the levels of the biomarkers can be compared to time-matched reference values for infected or non-infected subjects.

In any embodiment, the non-infectious inflammatory condition can be selected from the group of systemic inflammatory response syndrome (SIRS), an autoimmune disorder, a traumatic injury, and surgery.

In any embodiment, the patient can be a human being.

5 In any embodiment, measuring the levels of the biomarkers can include performing microarray analysis, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), a Northern blot, or a serial analysis of gene expression (SAGE).

In one embodiment, the invention is drawn to a kit including agents for measuring 10 the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB biomarkers.

In any embodiment, the kit can include agents for measuring the levels of CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers

In any embodiment, the kit can include a microarray.

15 In any embodiment, the microarray can include an oligonucleotide that hybridizes to an IFI27 polynucleotide, an oligonucleotide that hybridizes to a JUP polynucleotide, an oligonucleotide that hybridizes to a LAX1 polynucleotide, an oligonucleotide that hybridizes to a HK3 polynucleotide, an oligonucleotide that hybridizes to a TNIP1 polynucleotide, an oligonucleotide that hybridizes to a GPAA1 polynucleotide, and an 20 oligonucleotide that hybridizes to a CTSB polynucleotide.

In any embodiment the microarray can include an oligonucleotide that hybridizes to a CEACAM1 polynucleotide, an oligonucleotide that hybridizes to a ZDHHC19 polynucleotide, an oligonucleotide that hybridizes to a C9orf95 polynucleotide, an oligonucleotide that hybridizes to a GNA15 polynucleotide, an oligonucleotide that 25 hybridizes to a BATF polynucleotide, an oligonucleotide that hybridizes to a C3AR1 polynucleotide, an oligonucleotide that hybridizes to a KIAA1370 polynucleotide, an oligonucleotide that hybridizes to a TGFBI polynucleotide, an oligonucleotide that hybridizes to a MTCH1 polynucleotide, an oligonucleotide that hybridizes to a RPGRIP1 polynucleotide, and an oligonucleotide that hybridizes to a HLA-DPB1 polynucleotide.

30 In any embodiment, the kit can include information, in electronic or paper form, with instructions to correlate the detected levels of each biomarker with sepsis.

In one embodiment, the method is drawn to a computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps of: (a) receiving inputted patient data including values for the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB biomarkers in a biological sample from the patient; b) analyzing the level of each of the biomarkers and comparing with respective reference value ranges for the biomarkers; c) calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and (d) displaying information regarding the diagnosis of the patient.

In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

In one embodiment, the invention is drawn to a diagnostic system for performing the computer implemented method, the diagnostic system including a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein; b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and (c) a display component for displaying information regarding the diagnosis of the patient.

In any embodiment, the storage component can include instructions for calculating the bacterial/viral metascore.

In one embodiment, the invention is drawn to a computer implemented method for diagnosing a patient having inflammation, the computer performing steps of: a) receiving inputted patient data including values for the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in a biological sample from the patient; b) analyzing the levels of each of the biomarkers and comparing with respective reference value ranges for the biomarkers; c) calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection,

and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition; d) calculating a bacterial/viral metascore for the patient if the sepsis score indicates that the patient has an infection, wherein a positive bacterial/viral metascore for the patient
5 indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and e displaying information regarding the diagnosis of the patient.

In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

10 In one embodiment, the invention is drawn to a diagnostic system for performing the computer implemented method, the diagnostic system including a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein; b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and
15 configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and c) a display component for displaying information regarding the diagnosis of the patient.

In any embodiment, the storage component can include instructions for calculating the sepsis metascore and the bacterial/viral metascore.

20 In one embodiment, the invention is drawn to a method for diagnosing and treating an infection in a patient, the method including: a) obtaining a biological sample from the patient; b) measuring the levels of expression of a set of viral response genes and a set of bacterial response genes in the biological sample, wherein the set of viral response genes includes one or more genes selected from the group of OAS2, CUL1,
25 ISG15, CHST12, IFIT1, SIGLEC1, ADA, MX1, RSAD2, IFI44L, GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, HERC5, IFIH1, SAMD9, IFI6, IFIT3, IFIT5, XAF1, ISG20, PARP12, IFIT2, DHX58, STAT1, and the set of bacterial response genes includes one or more genes selected from the group of SLC12A9, ACPP, STAT5B, EMR1, FLII, PTAFR, NRD1, PLP2, DYSF,
30 TWF2, SORT1, TSPO, TBXAS1, ACAA1, S100A12, PGD, LAPTM5, NINJ2, DOK3, SORL1, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT,

CYBRD1; and c) analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for a noninfected control subject, wherein differential expression of the viral response genes compared to the reference value.

In any embodiment, the set of viral response genes and the set of bacterial response genes can be selected from the group of: a) a set of viral response genes including OAS2 and CUL1 and a set of bacterial response genes including SLC12A9, ACPP, STAT5B; b) a set of viral response genes including ISG15 and CHST12 and a set of bacterial response genes including EMR1 and FLII; c) a set of viral response genes including IFIT1, SIGLEC1, and ADA and a set of bacterial response genes including PTAFR, NRD1, PLP2; d) a set of viral response genes including MX1 and a set of bacterial response genes including DYSF, TWF2; e) a set of viral response genes including RSAD2 and a set of bacterial response genes including SORT1 and TSPO; f) a set of viral response genes including IFI44L, GZMB, and KCTD14 and a set of bacterial response genes including TBXAS1, ACAA1, and S100A12; g) a set of viral response genes including LY6E and a set of bacterial response genes including PGD and LAPTM5; h) a set of viral response genes including IFI44, HESX1, and OASL and a set of bacterial response genes including NINJ2, DOK3, SORL1, and RAB31; and i) a set of viral response genes including OAS1 and a set of bacterial response genes including IMPA2 and LTA4H.

In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

In any embodiment, the levels of the biomarkers can be compared to time-matched reference values for infected or non-infected subjects.

In any embodiment, the method can include calculating a bacterial/viral metascore for the patient t based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

In any embodiment, the method can include measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1

biomarkers in the biological sample; and analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, wherein increased levels of expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection.

In one embodiment, the invention is drawn to a kit including agents for measuring the levels of expression of a set of viral response genes and a set of bacterial response genes selected from the group of: (a) a set of viral response genes including OAS2 and CUL1 and a set of bacterial response genes including SLC12A9, ACPP, STAT5B; (b) a set of viral response genes including ISG15 and CHST12 and a set of bacterial response genes including EMR1 and FLII; b) a set of viral response genes including IFIT1, SIGLEC1, and ADA and a set of bacterial response genes including PTAFR, NRD1, PLP2; c) a set of viral response genes including MX1 and a set of bacterial response genes including DYSF, TWF2; d) a set of viral response genes including RSAD2 and a set of bacterial response genes including SORT1 and TSPO; e) a set of viral response genes including IFI44L, GZMB, and KCTD14 and a set of bacterial response genes including TBXAS1, ACAA1, and S100A12; f) a set of viral response genes including LY6E and a set of bacterial response genes including PGD and LAPTM5; g) a set of viral response genes including IFI44, HESX1, and OASL and a set of bacterial response genes including NINJ2, DOK3, SORL1, and RAB31; and h) a set of viral response genes including OAS1 and a set of bacterial response genes including IMPA2 and LTA4H.

In any embodiment, the kit can include a microarray.

In one embodiment, the invention is drawn to a computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps of: a) receiving inputted patient data including values for the levels of expression in a biological sample of a set of viral response genes and a set of bacterial response genes in

the biological sample, wherein the set of viral response genes includes one or more genes selected from the group of OAS2, CUL1, ISG15, CHST12, IFIT1, SIGLEC1, ADA, MX1, RSAD2, IFI44L, GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, HERC5, IFIH1, SAMD9, IFI6, IFIT3, IFIT5, XAF1,
5 ISG20, PARP12, IFIT2, DHX58, STAT1, and the set of bacterial response genes includes one or more genes selected from the group of SLC12A9, ACPP, STAT5B, EMR1, FLII, PTAFR, NRD1, PLP2, DYSF, TWF2, SORT1, TSPO, TBXAS1, ACAA1, S100A12, PGD, LAPTM5, NINJ2, DOK3, SORL1, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT, CYBRD1; b) analyzing the levels of
10 expression of the set of viral response genes and the set of bacterial response genes and comparing with respective reference value ranges for a noninfected control subject; c) calculating a bacterial/viral metascore for the patient based on the levels of expression of the set of viral response genes and the set of bacterial response genes; and (d) displaying information regarding the diagnosis of the patient.

15 In one embodiment, the invention is drawn to a diagnostic system for performing the computer implemented method, the diagnostic system including a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein; b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and
20 configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and c) a display component for displaying information regarding the diagnosis of the patient.

In one embodiment, the invention includes a method for diagnosing an infection in a patient, including (a) measuring levels of expression of at least two biomarkers in a
25 biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers include at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2,
30 IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1,

PTAFR, and LAPTM5; and wherein the second set of biomarkers include at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20,
5 DHX58, EIF2AK2, XAF1, and GZMB; and (b) analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers to determine a viral or bacterial infection.

In any embodiment, the method can include administering an effective amount of an anti-viral agent to the patient if the patient is diagnosed with a viral infection or
10 administering an effective amount of an antibiotic to the patient if the patient is diagnosed with a bacterial infection.

In any embodiment, the levels of expression of the at least two biomarkers can provide an area under a curve of at least 0.80.

In any embodiment, the first set of biomarkers can include at least one of HK3,
15 TNIP1, GPAA1, and CTSB; and the second set of biomarkers can include at least one of IFI27, JUP, and LAX1.

In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

In any embodiment, the levels of the biomarkers can be compared to time-
20 matched reference values for infected or non-infected subjects.

In any embodiment, the method can include calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a
25 bacterial infection.

In any embodiment, the method can include normalizing data using COCONUT normalization; COCONUT normalization including the steps of (a) separating data from multiple cohorts into healthy and diseased components; (b) co-normalizing the healthy components using ComBat co-normalization without covariates; (c) obtaining ComBat
30 estimated parameters for each dataset for the healthy component; and (d) applying the ComBat estimated parameters onto the diseased component.

In any embodiment, the patient can be a human being.

In any embodiment, measuring the level of the plurality of biomarkers can include performing microarray analysis, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), a Northern blot, or a serial analysis of gene
5 expression (SAGE).

In one embodiment, the invention can include a method of diagnosing and treating a patient having inflammation, the method including the steps of (a) measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1,
10 and HLA-DPB1 biomarkers in a biological sample of the patient; (b) first analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, wherein increased levels of expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers
15 compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection; and; (c) further analyzing the
20 levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers include at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD,
25 S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers include at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2,
30 RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1,

JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB to determine a bacterial or viral infection.

In any embodiment, the method can include calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition.

In any embodiment, the method can include calculating a bacterial/viral metascore for the patient if the patient is diagnosed as having an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

In any embodiment, the levels of the biomarkers can be compared to time-matched reference values for infected or non-infected subjects.

In any embodiment, the non-infectious inflammatory condition can be selected from the group of systemic inflammatory response syndrome (SIRS), an autoimmune disorder, a traumatic injury, and surgery.

In any embodiment, the patient can be a human being.

In any embodiment, measuring the levels of the biomarkers can include performing microarray analysis, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), a Northern blot, or a serial analysis of gene expression (SAGE).

In one embodiment, the method is drawn to a kit, the kit including agents for measuring the levels of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection wherein the first set of biomarkers includes at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein

the second set of biomarkers includes at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and
5 GZMB.

In any embodiment, the kit can include agents for measuring the levels of CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers.

In any embodiment, the kit can include a microarray.

10 In any embodiment, the microarray can include an oligonucleotide that hybridizes to an IFI27 polynucleotide, an oligonucleotide that hybridizes to a JUP polynucleotide, an oligonucleotide that hybridizes to a LAX1 polynucleotide, an oligonucleotide that hybridizes to a HK3 polynucleotide, an oligonucleotide that hybridizes to a TNIP1 polynucleotide, an oligonucleotide that hybridizes to a GPAA1 polynucleotide, and an
15 oligonucleotide that hybridizes to a CTSB polynucleotide.

In any embodiment, the microarray can include an oligonucleotide that hybridizes to a CEACAM1 polynucleotide, an oligonucleotide that hybridizes to a ZDHHC19 polynucleotide, an oligonucleotide that hybridizes to a C9orf95 polynucleotide, an oligonucleotide that hybridizes to a GNA15 polynucleotide, an oligonucleotide that
20 hybridizes to a BATF polynucleotide, an oligonucleotide that hybridizes to a C3AR1 polynucleotide, an oligonucleotide that hybridizes to a KIAA1370 polynucleotide, an oligonucleotide that hybridizes to a TGFBI polynucleotide, an oligonucleotide that hybridizes to a MTCH1 polynucleotide, an oligonucleotide that hybridizes to a RPGRIP1 polynucleotide, and an oligonucleotide that hybridizes to a HLA-DPB1 polynucleotide.

25 In any embodiment, the kit can include information, in electronic or paper form, having instructions to correlate the detected levels of each biomarker with sepsis.

In one embodiment, the invention is drawn to a computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps of: (a) receiving inputted patient data including values for the levels of at least two
30 biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a

bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers include at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers include at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB biomarkers in the biological sample from the patient; (b) analyzing the level of each of the biomarkers and comparing with respective reference value ranges for the biomarkers; (c) calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and (d) displaying information regarding the diagnosis of the patient.

In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

In one embodiment, the invention is drawn to a diagnostic system carrying out the computer implemented method, including (a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein; (b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and (c) a display component for displaying information regarding the diagnosis of the patient.

In any embodiment, the storage component can include instructions for calculating the bacterial/viral metascore.

In one embodiment, the invention is drawn to a computer implemented method for diagnosing a patient having inflammation, the computer performing the steps of (a)

receiving inputted patient data having values for the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in a biological sample from the patient; (b) analyzing the levels of each of the biomarkers and
5 comparing with respective reference value ranges for the biomarkers; (c) calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory
10 condition; (d) calculating a bacterial/viral metascore for the patient if the sepsis score indicates that the patient has an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and (e) displaying information regarding the diagnosis of the patient.

15 In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

In one embodiment, the invention is drawn to a diagnostic system carrying out the computer implemented method, including (a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the
20 patient stored therein; (b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and (c) a display component for displaying information regarding the diagnosis of the patient.

25 In any embodiment, the storage component can include instructions for calculating the sepsis metascore and the bacterial/viral metascore.

In one embodiment, the invention is drawn to a method for diagnosing and treating an infection in a patient, the method including (a) obtaining a biological sample from the patient; (b) measuring the levels of expression of any set of at least two
30 biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a

bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers include at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers include at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB; and (c) analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for a noninfected control subject, wherein differential expression of the viral response genes compared to the reference value ranges for a noninfected control subject indicate that the patient has a viral infection, and differential expression of the bacterial response genes compared to the reference value ranges for a noninfected control subject indicate that the patient has a bacterial infection.

In any embodiment, the set of viral and bacterial response genes can be selected from the group of: (a) a set of viral response genes including OAS2 and CUL1 and a set of bacterial response genes including SLC12A9, ACPP, STAT5B; (b) a set of viral response genes including ISG15 and CHST12 and a set of bacterial response genes including EMR1 and FLII; (c) a set of viral response genes including IFIT1, SIGLEC1, and ADA and a set of bacterial response genes including PTAFR, NRD1, PLP2; (d) a set of viral response genes including MX1 and a set of bacterial response genes including DYSF, TWF2; (e) a set of viral response genes including RSAD2 and a set of bacterial response genes including SORT1 and TSPO; (f) a set of viral response genes including IFI44L, GZMB, and KCTD14 and a set of bacterial response genes including TBXAS1, ACAA1, and S100A12; (g) a set of viral response genes including LY6E and a set of bacterial response genes including PGD and LAPTM5; (h) a set of viral response genes including IFI44, HESX1, and OASL and a set of bacterial response genes including NINJ2, DOK3, SORL1, and RAB31; and (i) a set of viral response genes including OAS1 and a set of bacterial response genes including IMPA2 and LTA4H.

In any embodiment, the biological sample can include whole blood or peripheral blood mononucleated cells (PBMCS).

In any embodiment, the levels of the biomarkers can be compared to time-matched reference values for infected or non-infected subjects.

5 In any embodiment, the method can include calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

10 In any embodiment, the method can include measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in the biological sample; and analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, 15 wherein increased levels of expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, 20 C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection.

In one embodiment, the method is drawn to a kit, the kit including agents for measuring the levels of expression of a set of viral response genes and a set of bacterial 25 response genes selected from (a) a set of viral response genes including OAS2 and CUL1 and a set of bacterial response genes including SLC12A9, ACPP, STAT5B; (b) a set of viral response genes including ISG15 and CHST12 and a set of bacterial response genes including EMR1 and FLII; (c) a set of viral response genes including IFIT1, SIGLEC1, and ADA and a set of bacterial response genes including PTAFR, NRD1, PLP2; (d) a set 30 of viral response genes including MX1 and a set of bacterial response genes including DYSF, TWF2; (e) a set of viral response genes including RSAD2 and a set of bacterial

response genes including SORT1 and TSPO; (f) a set of viral response genes including IFI44L, GZMB, and KCTD14 and a set of bacterial response genes including TBXAS1, ACAA1, and S100A12; (h) a set of viral response genes including IFI44, HESX1, and OASL and a set of bacterial response genes including NINJ2, DOK3, SORL1, and
5 RAB31; and (i) a set of viral response genes including OAS1 and a set of bacterial response genes including IMPA2 and LTA4H.

In any embodiment, the kit can include a microarray.

In one embodiment, the invention is drawn to a computer implemented method for diagnosing a patient suspected of having an infection, the computer performing the
10 steps of (a) receiving inputted patient data including values for the levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection, wherein the set of viral response
15 genes includes one or more genes selected from the group of OAS2, CUL1, ISG15, CHST12, IFIT1, SIGLEC1, ADA, MX1, RSAD2, IFI44L, GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, HERC5, IFIH1, SAMD9, IFI6, IFIT3, IFIT5, XAF1, ISG20, PARP12, IFIT2, DHX58, STAT1, and the set of bacterial response genes includes one or more genes selected from the group of
20 SLC12A9, ACPP, STAT5B, EMR1, FLII, PTAFR, NRD1, PLP2, DYSF, TWF2, SORT1, TSPO, TBXAS1, ACAA1, S100A12, PGD, LAPTM5, NINJ2, DOK3, SORL1, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT, CYBRD1; (b) analyzing the levels of expression of the set of viral response genes and the set of bacterial response genes and comparing with respective reference value ranges for
25 a noninfected control subject; (c) calculating a bacterial/viral metascore for the patient based on the levels of expression of the set of viral response genes and the set of bacterial response genes; and (d) displaying information regarding the diagnosis of the patient.

In one embodiment, the invention is drawn to a diagnostic system performing the computer implemented method, the diagnostic system including (a) a storage component
30 for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein; (b) a computer processor for processing data,

wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and (c) a display component for displaying information regarding the diagnosis of the patient.

5 These and other embodiments of the subject invention will readily occur to those of skill in the art in view of the disclosure herein.

Brief Description of the Figures

FIGS. 1A and 1B show summary Receiver Operating Characteristic (ROC)
10 curves for (FIG. 1A) discovery and (FIG. 1B) direct validation datasets for the bacterial/viral metascore. A summary ROC curve is shown in black, with 95% confidence intervals in dark grey.

FIG. 2 shows bacterial/viral scores for COCONUT co-normalized whole blood discovery datasets. PBMCs datasets are left out of FIG. 2 because PBMC datasets are
15 expected to have different gene levels than whole blood. The global AUC across all whole blood discovery datasets is 0.92. Score distribution by dataset (dark gray = bacterial, light gray = viral), individual gene levels, and housekeeping genes (greyscale) are shown. The dotted line shows a possible global threshold. The width of each violin corresponds to the distribution of scores within the given dataset. The vertical bar within
20 each violin spans the 25th-75th percentile, and the middle white dash shows the mean score. Housekeeping genes (POLG, ATP6V1B1, and PEG10) show expected invariance across datasets post-COCONUT-normalization.

FIGS. 3A-3C show an integrated antibiotics decision model (IADM) across COCONUT-co-normalized public gene expression data that matched inclusion criteria.
25 FIG. 3A shows an IADM schematic. FIG. 3B shows a distribution of scores and cutoffs for IADM in COCONUT-co-normalized data. FIG. 3C shows a confusion matrix for diagnosis. Bacterial infection sensitivity: 94.0%; Bacterial infection specificity: 59.8%; Viral infection sensitivity: 53.0%; Viral infection specificity: 90.6%.

FIGS. 4A-4E show targeted NanoString gene expression data from children with
30 SIRS/sepsis from the GPSSSI cohort never tested with microarrays (total N=96, of which SIRS=36, bacterial sepsis=49, viral sepsis=11). FIG. 4A shows the breakdown of infected

patients by organism type. FIGS. 4B and 4C show ROC curves for the SMS and the bacterial/viral metascore. FIG. 4D shows the distribution of scores and cutoffs for IADM. FIG. 4E shows a confusion matrix for IADM; Bacterial infection sensitivity: 89.7%; Bacterial infection specificity: 70.0%; Viral infection sensitivity: 54.5%; Viral infection
5 specificity: 96.5%.

FIGS. 5A and 5B show that the Sepsis MetaScore (SMS) alone cannot determine pathogen type. Diagram in (FIG. 5A) indicates how a decision model could be built. FIG. 5B shows the distribution of SMS in patients with bacterial versus viral infections. Of 11 datasets, there were only three for which the SMS distribution showed a significant
10 difference between bacterial and viral infections.

FIG. 6 shows a schematic of the workflow for the multi-cohort analysis and discovery of the bacterial-viral metasignature.

FIG. 7 shows Forest plots of the genes in the bacterial/viral metascore across the discovery datasets. The *x* axes represent standardized mean difference between bacterial
15 and viral infection samples, computed as Hedges' *g*, in log2 scale. The size of the black rectangles is inversely proportional to the standard error of mean in the study. Whiskers represent the 95% confidence interval. The light gray diamonds represent overall, combined mean difference for a given gene. Width of the diamonds represents the 95% confidence interval of overall combined mean difference.

20 FIG. 8 shows Forest plots of the random-effects meta-analysis of the summary ROC parameters alpha and beta for the discovery datasets. Alpha roughly controls the distance from the line of identity (higher alpha = higher AUC) and beta controls the skew of the actual ROC curve (beta = 0 means no skew).

FIG. 9 shows Forest plots of the random-effects meta-analysis of the summary
25 ROC parameters alpha and beta for the validation datasets. Alpha roughly controls the distance from the line of identity (higher alpha = higher AUC) and beta controls the skew of the actual ROC curve (beta = 0 means no skew).

FIG. 10 shows the bacterial/viral metascore ROC in GSE53166, monocyte-derived dendritic cells stimulated *in vitro* with LPS or influenza virus, total N = 75 (39
30 LPS, 36 influenza virus).

FIG. 11 shows a schematic of COCONUT co-normalization. Light gray indicates healthy ('H'), medium gray means viral ('V') and dark gray means bacterial ('B'). Different crosshatchings are meant to indicate different batch effects. See Methods for formal mathematical details.

5 FIGS. 12A and 12B show data of whole blood discovery datasets. PBMCs datasets are left out of FIGs. 12A and 12B because PBMC datasets are expected to have different gene levels than whole blood. FIG. 12A shows raw data and FIG. 12B shows COCONUT co-normalized data. COCONUT co-normalization resets each gene to be at the same location and scale for control patients. Distribution of a gene within a dataset is 10 unchanged (median difference in T-statistics for healthy versus disease within datasets is 0, range (-1e-13, 1e-13), across all genes and all datasets). Housekeeping gene ATP6V1B1 exhibits expected invariance with respect to disease, and is invariant across datasets after normalization. A gene expected to be induced by disease, e.g., CEACAM1, exhibits invariance across healthy controls, but can vary in disease states between 15 datasets. Upper color bars indicate datasets; lower color bar indicate disease class.

FIG. 13 shows the bacterial/viral score in global ROC of COCONUT co-normalization of whole blood validation datasets. The global AUC across all whole blood validation datasets is 0.93. The score distribution by dataset (dark gray violins = bacterial, light gray violins = viral) and housekeeping genes (greyscale) are shown. The width of 20 each violin corresponds to the distribution of scores within the given dataset. The vertical bar within each violin spans the 25th-75th percentile, and the middle white dash shows the mean score. The dotted line shows a possible global threshold. Housekeeping genes (POLG, ATP6V1B1, and PEG10) show expected invariance across datasets post-COCONUT-normalization.

25 FIG. 14 shows the bacterial/viral score in global ROC of non-co-normalized whole blood discovery datasets. PBMCs datasets are left out of FIG. 14 because PBMC datasets are expected to have different gene levels than whole blood. The global AUC across all whole blood discovery datasets is 0.93. The score distribution by dataset (dark gray violins = bacterial, light gray violins = viral) and housekeeping genes (greyscale) are 30 shown. The width of each violin corresponds to the distribution of scores within the given dataset. The vertical bar within each violin spans the 25th-75th percentile, and the middle

white dash shows the mean score. Note the highly varying locations and scales of the housekeeping genes POLG, ATP6V1B1, and PEG10.

FIG. 15 shows the bacterial/viral score in global ROC of non-co-normalized whole blood validation datasets. PBMCs datasets are left out of FIG. 15 because PBMC datasets are expected to have different gene levels than whole blood. The score distribution by dataset (dark gray violins = bacterial, light gray violins = viral) and housekeeping genes (greyscale) are shown. The width of each violin corresponds to the distribution of scores within the given dataset. The vertical bar within each violin spans the 25th-75th percentile, and the middle white dash shows the mean score. Note the highly varying locations and scales of the housekeeping genes POLG, ATP6V1B1, and PEG10.

FIG. 16 shows the bacterial/viral score in global ROC of COCONUT co-normalization of PBMC validation datasets. PBMCs datasets are examined separately because PBMC datasets are expected to have different gene levels than whole blood. The global AUC across all PBMC validation datasets is 0.92. The score distribution by dataset (dark gray violins = bacterial, light gray violins = viral) and housekeeping genes (greyscale) are shown. The dotted line shows a possible global threshold. The width of each violin corresponds to the distribution of scores within the given dataset. The vertical bar within each violin spans the 25th-75th percentile, and the middle white dash shows the mean score. Housekeeping genes (POLG, ATP6V1B1) show expected invariance across datasets post-COCONUT-normalization.

FIG. 17 shows the bacterial/viral score in global ROC of non-co-normalized PBMC validation datasets. PBMCs datasets are examined separately because PBMC datasets are expected to have different gene levels than whole blood. The score distribution by dataset (dark gray violins = bacterial, light gray violins = viral), individual gene levels, housekeeping genes (greyscale) are shown. The width of each violin corresponds to the distribution of scores within the given dataset. The vertical bar within each violin spans the 25th-75th percentile, and the middle white dash shows the mean score. Note the highly varying locations and scales of the housekeeping genes POLG and ATP6V1B1.

FIG. 18 shows the distribution of mean AUCs across all discovery datasets for 10,000 randomly chosen 2-gene pairs.

FIGS. 19A-19D show the effects of age on the Sepsis MetaScore in COCONUT co-normalized data. FIG. 19A shows age versus SMS by pathogen type, to assess whether pathogen type is driving age differences in SMS. FIG. 19B shows the log10(age) vs. SMS by pathogen type, showing that at extremes of age, the SMS may have a different attainable maximum. FIG. 19C shows the log10(age) versus SMS by dataset, demonstrating that the relationship between age and SMS is dataset-independent. FIGS. 19A-19C only include infected patient samples; FIG. 19D shows both healthy and noninfected SIRS samples in addition to show the baseline across ages. In all cases, the GSE25504 age data are randomly distributed according to the mean age given in their manuscript, roughly 2 weeks +/- 1 week, to show data density. All ages=0 were reset as age=1/365.

FIGS. 20A and 20B show the Sepsis MetaScore across all whole blood data (both discovery and validation) before (FIG. 20B) and after COCONUT co-normalization (FIG. 20A). The global AUC is 0.86 (95% CI 0.84-0.89) after COCONUT co-normalization. The score distribution by dataset (light gray violins = non-infected inflammation, dark gray violins = infections/sepsis) and housekeeping genes (greyscale) are shown. The dotted line shows a possible global threshold. The width of each violin corresponds to the distribution of scores within the given dataset. The vertical bar within each violin spans the 25th-75th percentile, and the middle white dash shows the mean score. Note the invariance of the housekeeping genes POLG, ATP6V1B1, and PEG10 across datasets in FIG. 20A post-COCONUT-normalization, with highly varying locations and scales of the housekeeping genes prior to normalization in Fig 20B.

FIGS. 21A and 21B show the IADM across COCONUT-co-normalized public gene expression data including healthy controls. The included datasets (and the score cutoffs used) are the same as those in FIGS. 3A-3C. FIG. 21A shows the distribution of scores for IADM in COCONUT-co-normalized data. FIG. 21B shows a confusion matrix for diagnosis. Bacterial infection sensitivity: 94.2%; Bacterial infection specificity: 68.5%; Viral infection sensitivity: 53.0%; Viral infection specificity: 94.1%. 'SIRS' refers to non-infected inflammation.

FIG. 22 shows NPV and PPV versus prevalence for a diagnostic test with 94.0% sensitivity and 59.8% specificity. Red lines show an NPV of 98.3% at a prevalence of 15%, as a rough estimate for real case-rates of infection.

FIGS. 23A-23D show results for the GSE63990 dataset (adults with acute respiratory infections). FIGS. 23A and 23B show ROC curves for the Sepsis MetaScore and the bacterial/viral metascore. FIG. 23C shows the distribution of scores and cutoffs for IADM. FIG. 23D shows a confusion matrix for IADM; Bacterial infection sensitivity: 94.3%; Bacterial infection specificity: 52.2%; Viral infection sensitivity: 52.2%; Viral infection specificity: 94.3%.

DETAILED DESCRIPTION

The practice of the present invention will employ, unless otherwise indicated, conventional methods of pharmacology, chemistry, biochemistry, recombinant DNA techniques and immunology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., J.E. Bennett, R. Dolin, and M.J. Blaser *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* (Saunders, 8th edition, 2014); J.R. Brown *Sepsis: Symptoms, Diagnosis and Treatment* (Public Health in the 21st Century Series, Nova Science Publishers, Inc., 2013); *Sepsis and Non-infectious Systemic Inflammation: From Biology to Critical Care* (J. Cavaillon, C. Adrie eds., Wiley-Blackwell, 2008); *Sepsis: Diagnosis, Management and Health Outcomes* (Allergies and Infectious Diseases, N. Khardori ed., Nova Science Pub Inc., 2014); *Handbook of Experimental Immunology*, Vols. I-IV (D.M. Weir and C.C. Blackwell eds., Blackwell Scientific Publications); A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition); Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001); *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.).

All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entireties.

I. DEFINITIONS

In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a biomarker" includes a mixture of two or more biomarkers, and the like.

The term "about," particularly in reference to a given quantity, is meant to encompass deviations of plus or minus five percent.

The term Area Under the Curve (AUC) as used herein will be understood to refer to the area under a Receiving Operating Characteristic Curve (ROC Curve).

A "biomarker" in the context of the present invention refers to a biological compound, such as a polynucleotide which is differentially expressed in a sample taken from patients having an infection as compared to a comparable sample taken from control subjects (e.g., a person with a negative diagnosis, normal or healthy subject, or non-infected subject). The biomarker can be a nucleic acid, a fragment of a nucleic acid, a polynucleotide, or an oligonucleotide that can be detected and/or quantified. Biomarkers include polynucleotides comprising nucleotide sequences from genes or RNA transcripts of genes, including but not limited to, IFI27, JUP, LAX1, OAS2, CUL1, ISG15, CHST12, IFIT1, SIGLEC1, ADA, MX1, RSAD2, IFI44L, GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, HERC5, IFIH1, SAMD9, IFI6, IFIT3, IFIT5, XAF1, ISG20, PARP12, IFIT2, DHX58, STAT1, HK3, TNIP1, GPAA1, CTSB, SLC12A9, ACPP, STAT5B, EMR1, FLII, PTAFR, NRD1, PLP2, DYSF, TWF2, SORT1, TSPO, TBXAS1, ACAA1, S100A12, PGD, LAPTM5, NINJ2, DOK3, SORL1, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT, CYBRD1, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1.

"Viral response genes" refer to genes that are differentially expressed in a sample taken from patients having a viral infection as compared to a comparable sample taken from control subjects (e.g., a person with a negative diagnosis, normal or healthy subject, or non-infected subject). Viral response genes include, but are not limited to, IFI27, JUP,

LAX1, OAS2, CUL1, ISG15, CHST12, IFIT1, SIGLEC1, ADA, MX1, RSAD2, IFI44L, GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, HERC5, IFIH1, SAMD9, IFI6, IFIT3, IFIT5, XAF1, ISG20, PARP12, IFIT2, DHX58, and STAT1.

5 "Bacterial response genes" refer to genes that are differentially expressed in a sample taken from patients having a bacterial infection as compared to a comparable sample taken from control subjects (e.g., a person with a negative diagnosis, normal or healthy subject, or non-infected subject). Bacterial response genes include, but are not limited to, HK3, TNIP1, GPAA1, CTSB, SLC12A9, ACPP, STAT5B, EMR1, FLII,
10 PTAFR, NRD1, PLP2, DYSF, TWF2, SORT1, TSPO, TBXAS1, ACAA1, S100A12, PGD, LAPTM5, NINJ2, DOK3, SORL1, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT, and CYBRD1.

"Sepsis response genes" refer to genes that are differentially expressed in a sample taken from patients having sepsis or an infection as compared to a comparable
15 sample taken from control subjects (e.g., a person with a negative diagnosis, normal or healthy subject, or non-infected subject). Sepsis response genes include, but are not limited to, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1.

The terms "polypeptide" and "protein" refer to a polymer of amino acid residues
20 and are not limited to a minimum length. Thus, peptides, oligopeptides, dimers, multimers, and the like, are included within the definition. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include postexpression modifications of the polypeptide, for example, glycosylation, acetylation, phosphorylation, hydroxylation, oxidation, and the like.

25 The terms "polynucleotide," "oligonucleotide," "nucleic acid" and "nucleic acid molecule" are used herein to include a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. This term refers only to the primary structure of the molecule. Thus, the term includes triple-, double- and single-stranded DNA, as well as triple-, double- and single-stranded RNA. It also includes modifications, such as
30 by methylation and/or by capping, and unmodified forms of the polynucleotide. More particularly, the terms "polynucleotide," "oligonucleotide," "nucleic acid" and "nucleic

acid molecule" include polydeoxyribonucleotides (containing 2-deoxy-D-ribose), polyribonucleotides (containing D-ribose), and any other type of polynucleotide which is an N- or C-glycoside of a purine or pyrimidine base. There is no intended distinction in length between the terms "polynucleotide," "oligonucleotide," "nucleic acid" and "nucleic
5 acid molecule," and these terms are used interchangeably.

The phrase "differentially expressed" refers to differences in the quantity and/or the frequency of a biomarker present in a sample taken from patients having, for example, an infection (e.g., viral infection or bacterial infection) as compared to a control subject or non-infected subject. For example, a biomarker can be a polynucleotide which
10 is present at an elevated level or at a decreased level in samples of patients with an infection (e.g., viral infection or bacterial infection) compared to samples of control subjects. Alternatively, a biomarker can be a polynucleotide which is detected at a higher frequency or at a lower frequency in samples of patients with an infection (e.g., viral infection or bacterial infection) compared to samples of control subjects. A biomarker
15 can be differentially present in terms of quantity, frequency or both.

A polynucleotide is differentially expressed between two samples if the amount of the polynucleotide in one sample is statistically significantly different from the amount of the polynucleotide in the other sample. For example, a polynucleotide is differentially expressed in two samples if it is present at least about 120%, at least about 130%, at least
20 about 150%, at least about 180%, at least about 200%, at least about 300%, at least about 500%, at least about 700%, at least about 900%, or at least about 1000% greater than it is present in the other sample, or if it is detectable in one sample and not detectable in the other.

Alternatively or additionally, a polynucleotide is differentially expressed in two
25 sets of samples if the frequency of detecting the polynucleotide in samples of patients' suffering from sepsis, is statistically significantly higher or lower than in the control samples. For example, a polynucleotide is differentially expressed in two sets of samples if it is detected at least about 120%, at least about 130%, at least about 150%, at least about 180%, at least about 200%, at least about 300%, at least about 500%, at least about
30 700%, at least about 900%, or at least about 1000% more frequently or less frequently observed in one set of samples than the other set of samples.

A "similarity value" is a number that represents the degree of similarity between two things being compared. For example, a similarity value may be a number that indicates the overall similarity between a patient's expression profile using specific phenotype-related biomarkers and reference value ranges for the biomarkers in one or more control samples or a reference expression profile (e.g., the similarity to a "viral infection" expression profile or a "bacterial infection" expression profile). The similarity value may be expressed as a similarity metric, such as a correlation coefficient, or may simply be expressed as the expression level difference, or the aggregate of the expression level differences, between levels of biomarkers in a patient sample and a control sample or reference expression profile.

The terms "subject," "individual," and "patient," are used interchangeably herein and refer to any mammalian subject for whom diagnosis, prognosis, treatment, or therapy is desired, particularly humans. Other subjects may include cattle, dogs, cats, guinea pigs, rabbits, rats, mice, horses, and so on. In some cases, the methods of the invention find use in experimental animals, in veterinary application, and in the development of animal models for disease, including, but not limited to, rodents including mice, rats, and hamsters; and primates.

As used herein, a "biological sample" refers to a sample of tissue, cells, or fluid isolated from a subject, including but not limited to, for example, blood, buffy coat, plasma, serum, blood cells (e.g., peripheral blood mononucleated cells (PBMCS)), fecal matter, urine, bone marrow, bile, spinal fluid, lymph fluid, samples of the skin, external secretions of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, organs, biopsies and also samples of *in vitro* cell culture constituents, including, but not limited to, conditioned media resulting from the growth of cells and tissues in culture medium, e.g., recombinant cells, and cell components.

A "test amount" of a biomarker refers to an amount of a biomarker present in a sample being tested. A test amount can be either an absolute amount (e.g., μg/ml) or a relative amount (e.g., relative intensity of signals).

A "diagnostic amount" of a biomarker refers to an amount of a biomarker in a subject's sample that is consistent with a diagnosis of an infection (e.g., viral infection or

bacterial infection). A diagnostic amount can be either an absolute amount (e.g., μg/ml) or a relative amount (e.g., relative intensity of signals).

A "control amount" of a biomarker can be any amount or a range of amount which is to be compared against a test amount of a biomarker. For example, a control amount of a biomarker can be the amount of a biomarker in a person without an infection (e.g., viral infection or bacterial infection). A control amount can be either in absolute amount (e.g., μg/ml) or a relative amount (e.g., relative intensity of signals).

The term "antibody" encompasses polyclonal and monoclonal antibody preparations, as well as preparations including hybrid antibodies, altered antibodies, chimeric antibodies and, humanized antibodies, as well as: hybrid (chimeric) antibody molecules (see, for example, Winter et al. (1991) *Nature* 349:293-299; and U.S. Pat. No. 4,816,567); $F(ab')_2$ and F(ab) fragments; F_v molecules (noncovalent heterodimers, see, for example, Inbar et al. (1972) *Proc Natl Acad Sci USA* 69:2659-2662; and Ehrlich et al. (1980) *Biochem* 19:4091-4096); single-chain Fv molecules (sFv) (see, *e.g.*, Huston et al. (1988) *Proc Natl Acad Sci USA* 85:5879-5883); dimeric and trimeric antibody fragment constructs; minibodies (see, *e.g.*, Pack et al. (1992) *Biochem* 31:1579-1584; Cumber et al. (1992) *J Immunology* 149B:120-126); humanized antibody molecules (see, *e.g.*, Riechmann et al. (1988) *Nature* 332:323-327; Verhoeyan et al. (1988) *Science* 239:1534-1536; and U.K. Patent Publication No. GB 2,276,169, published 21 Sep. 1994); and, any functional fragments obtained from such molecules, wherein such fragments retain specific-binding properties of the parent antibody molecule.

"Detectable moieties" or "detectable labels" contemplated for use in the invention include, but are not limited to, radioisotopes, fluorescent dyes such as fluorescein, phycoerythrin, Cy-3, Cy-5, allophycoyanin, DAPI, Texas Red, rhodamine, Oregon green, Lucifer yellow, and the like, green fluorescent protein (GFP), red fluorescent protein (DsRed), Cyan Fluorescent Protein (CFP), Yellow Fluorescent Protein (YFP), Cerianthus Orange Fluorescent Protein (cOFP), alkaline phosphatase (AP), beta-lactamase, chloramphenicol acetyltransferase (CAT), adenosine deaminase (ADA), aminoglycoside phosphotransferase (neo^r, $G418^r$) dihydrofolate reductase (DHFR), hygromycin-B-phosphotransferase (HPH), thymidine kinase (TK), lacZ (encoding β-galactosidase), and xanthine guanine phosphoribosyltransferase (XGPRT), beta-glucuronidase (gus),

Placental Alkaline Phosphatase (PLAP), Secreted Embryonic alkaline phosphatase (SEAP), or firefly or bacterial luciferase (LUC). Enzyme tags are used with their cognate substrate. The terms also include color-coded microspheres of known fluorescent light intensities (see e.g., microspheres with xMAP technology produced by Luminex (Austin, TX); microspheres containing quantum dot nanocrystals, for example, containing different ratios and combinations of quantum dot colors (e.g., Qdot nanocrystals produced by Life Technologies (Carlsbad, CA); glass coated metal nanoparticles (see e.g., SERS nanotags produced by Nanoplex Technologies, Inc. (Mountain View, CA); barcode materials (see e.g., sub-micron sized striped metallic rods such as Nanobarcodes produced by Nanoplex Technologies, Inc.), encoded microparticles with colored bar codes (see e.g., CellCard produced by Vitra Bioscience, vitrabio.com), and glass microparticles with digital holographic code images (see e.g., CyVera microbeads produced by Illumina (San Diego, CA). As with many of the standard procedures associated with the practice of the invention, skilled artisans will be aware of additional labels that can be used.

"Developing a classifier" refers to using input variables to generate an algorithm or classifier capable of distinguishing between two or more states.

"Diagnosis" as used herein generally includes determination as to whether a subject is likely affected by a given disease, disorder or dysfunction. The skilled artisan often makes a diagnosis on the basis of one or more diagnostic indicators, i.e., a biomarker, the presence, absence, or amount of which is indicative of the presence or absence of the disease, disorder or dysfunction.

"Prognosis" as used herein generally refers to a prediction of the probable course and outcome of a clinical condition or disease. A prognosis of a patient is usually made by evaluating factors or symptoms of a disease that are indicative of a favorable or unfavorable course or outcome of the disease. It is understood that the term "prognosis" does not necessarily refer to the ability to predict the course or outcome of a condition with 100% accuracy. Instead, the skilled artisan will understand that the term "prognosis" refers to an increased probability that a certain course or outcome will occur; that is, that a course or outcome is more likely to occur in a patient exhibiting a given condition, when compared to those individuals not exhibiting the condition.

"Substantially purified" refers to nucleic acid molecules or proteins that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free, from other components with which they are naturally associated.

5

II. Modes of Carrying Out the Invention

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is for the
10 purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

Although a number of methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

15 The invention is based on the discovery of biomarkers that can be used for diagnosis of an infection (see Example 1). In particular, the invention relates to the use of biomarkers that can be used to determine whether a patient with acute inflammation has a bacterial or viral infection that would benefit from treatment with an antibiotic or antiviral agent. In order to further an understanding of the invention, a more detailed
20 discussion is provided below regarding the identified biomarkers and methods of using them in diagnosis and treatment of infections.

A. Biomarkers

Biomarkers that can be used in the practice of the invention include
25 polynucleotides comprising nucleotide sequences from genes or RNA transcripts of genes, including "viral response genes" that are differentially expressed in patients having a viral infection compared to control subjects (e.g., a person with a negative diagnosis, normal or healthy subject, or non-infected subject not having a viral infection), such as, but not limited to, IFI27, JUP, LAX1, OAS2, CUL1, ISG15, CHST12, IFIT1, SIGLEC1,
30 ADA, MX1, RSAD2, IFI44L, GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, HERC5, IFIH1, SAMD9, IFI6, IFIT3, IFIT5,

XAFI, ISG20, PARP12, IFIT2, DHX58, and STAT1; "bacterial response genes" that are differentially expressed in patients having a bacterial infection compared to control subjects (e.g., a person with a negative diagnosis, normal or healthy subject, or non-infected subject not having a bacterial infection), such as, but not limited to, HK3, TNIP1, GPAA1, CTSB, SLC12A9, ACPP, STAT5B, EMR1, FLII, PTAFR, NRD1, PLP2, DYSF, TWF2, SORT1, TSPO, TBXAS1, ACAA1, S100A12, PGD, LAPTM5, NINJ2, DOK3, SORL1, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT, and CYBRD1; and "sepsis response genes" that are differentially expressed in patients having sepsis or an infection compared to control subjects (e.g., a person with a negative diagnosis, normal or healthy subject, or non-infected subject not having sepsis), such as, but not limited to, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1.

In one aspect, the invention includes a method of diagnosing an infection in a patient. The method comprises a) obtaining a biological sample from the patient; b) measuring the levels of expression in the biological sample of a set of viral response genes that show differential expression associated with a viral infection and a set of bacterial response genes that show differential expression associated with a bacterial infection; and c) analyzing the levels of expression of the viral response genes and the bacterial response genes in conjunction with respective reference value ranges.

When analyzing the levels of biomarkers in a biological sample, the reference value ranges can represent the levels of one or more biomarkers found in one or more samples of one or more subjects without an infection (e.g., healthy subject or non-infected subject). Alternatively, the reference values can represent the levels of one or more biomarkers found in one or more samples of one or more subjects with a viral infection or a bacterial infection. In certain embodiments, the levels of the biomarkers are compared to time-matched reference values ranges for non-infected or infected subjects.

In certain embodiments, the set of viral response genes and the set of bacterial response genes are selected from the group consisting of: a) a set of viral response genes comprising IFI27, JUP, and LAX1 and a set of bacterial response genes comprising HK3, TNIP1, GPAA1, and CTSB; b) a set of viral response genes comprising OAS2 and CUL1

and a set of bacterial response genes comprising SLC12A9, ACPP, STAT5B; c) a set of viral response genes comprising ISG15 and CHST12 and a set of bacterial response genes comprising EMR1 and FLII; d) a set of viral response genes comprising IFIT1, SIGLEC1, and ADA and a set of bacterial response genes comprising PTAFR, NRD1, PLP2; e) a set of viral response genes comprising MX1 and a set of bacterial response genes comprising DYSF, TWF2; f) a set of viral response genes comprising RSAD2 and a set of bacterial response genes comprising SORT1 and TSPO; g) a set of viral response genes comprising IFI44L, GZMB, and KCTD14 and a set of bacterial response genes comprising TBXAS1, ACAA1, and S100A12; h) a set of viral response genes comprising LY6E and a set of bacterial response genes comprising PGD and LAPTM5; i) a set of viral response genes comprising IFI44, HESX1, and OASL and a set of bacterial response genes comprising NINJ2, DOK3, SORL1, and RAB31; and j) a set of viral response genes comprising OAS1 and a set of bacterial response genes comprising IMPA2 and LTA4H.

The biological sample obtained from the patient to be diagnosed is typically whole blood or blood cells (e.g., PBMCS), but can be any sample from bodily fluids, tissue or cells that contain the expressed biomarkers. A "control" sample, as used herein, refers to a biological sample, such as a bodily fluid, tissue, or cells that are not diseased. That is, a control sample is obtained from a normal or non-infected subject (e.g. an individual known to not have a viral infection, bacterial infection, sepsis, or inflammation). A biological sample can be obtained from a patient by conventional techniques. For example, blood can be obtained by venipuncture, and solid tissue samples can be obtained by surgical techniques according to methods well known in the art.

In certain embodiments, a panel of biomarkers is used for diagnosis of an infection. Biomarker panels of any size can be used in the practice of the invention. Biomarker panels for diagnosing an infection typically comprise at least 3 biomarkers and up to 30 biomarkers, including any number of biomarkers in between, such as 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, or 30 biomarkers. In certain embodiments, the invention includes a biomarker panel comprising at least 3, or at least 4, or at least 5, or at least 6, or at least 7, or at least 8, or

at least 9, or at least 10, or at least 11 or more biomarkers. Although smaller biomarker panels are usually more economical, larger biomarker panels (i.e., greater than 30 biomarkers) have the advantage of providing more detailed information and can also be used in the practice of the invention.

5 In certain embodiments, the invention includes a panel of biomarkers for diagnosing an infection comprising one or more polynucleotides comprising a nucleotide sequence from a gene or an RNA transcript of a gene selected from the group consisting of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB. In another embodiment, the panel of biomarkers further comprises one or more polynucleotides comprising a 10 nucleotide sequence from a gene or an RNA transcript of a gene selected from the group consisting of CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1.

In certain embodiments, biomarkers for distinguishing viral and bacterial infections, as described herein, are combined with additional biomarkers that are capable 15 of distinguishing whether inflammation in a subject is caused by an infection or a noninfectious source of inflammation (e.g., traumatic injury, surgery, autoimmune disease, thrombosis, or systemic inflammatory response syndrome (SIRS)). A first diagnostic test is used to determine whether the acute inflammation is caused by an infectious or non-infectious source, and if the source of inflammation is an infection, a 20 second diagnostic test is used to determine whether the infection is a viral infection or a bacterial infection that will benefit from treatment with either antiviral agents or antibiotics, respectively.

In one embodiment, the invention includes a method of diagnosing and treating a patient having inflammation, the method comprising: a) obtaining a biological sample 25 from the patient; b) measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in the biological sample; and c) first analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, wherein increased levels of expression of the 30 CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-

DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the
5 non-infected control subject indicates that the patient does not have an infection; d) second analyzing the levels of expression of the IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB biomarkers, if the patient is diagnosed as having an infection, wherein increased levels of expression of the IFI27, JUP, LAX1 biomarkers compared to reference value ranges for the biomarkers for a control subject indicate that the patient
10 has a viral infection, and increased levels of expression of the HK3, TNIP1, GPAA1, CTSB biomarkers compared to the reference value ranges for the biomarkers for the control subject indicate that the patient has a bacterial infection; and e) administering an effective amount of an anti-viral agent to the patient if the patient is diagnosed with a viral infection, or administering an effective amount of an antibiotic to the patient if the
15 patient is diagnosed with a bacterial infection.

In another embodiment, the method further comprises calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control
20 subject indicates that the patient has a non-infectious inflammatory condition.

In another embodiment, the method further comprises calculating a bacterial/viral metascore for the patient if the patient is diagnosed as having an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient
25 has a bacterial infection.

In another embodiment, the invention includes a method of treating a patient suspected of having an infection, the method comprising: a) receiving information regarding the diagnosis of the patient according to a method described herein; and b) administering a therapeutically effective amount of an anti-viral agent if the patient is
30 diagnosed with a viral infection or administering an effective amount of an antibiotic if the patient is diagnosed with a bacterial infection.

In certain embodiments, a patient diagnosed with a viral infection by a method described herein is administered a therapeutically effective dose of an antiviral agent, such as a broad-spectrum antiviral agent, an antiviral vaccine, a neuraminidase inhibitor (e.g., zanamivir (Relenza) and oseltamivir (Tamiflu)), a nucleoside analogue (e.g.,
5 acyclovir, zidovudine (AZT), and lamivudine), an antisense antiviral agent (e.g., phosphorothioate antisense antiviral agents (e.g., Fomivirsen (Vitravene) for cytomegalovirus retinitis), morpholino antisense antiviral agents), an inhibitor of viral uncoating (e.g., Amantadine and rimantadine for influenza, Pleconaril for rhinoviruses), an inhibitor of viral entry (e.g., Fuzeon for HIV), an inhibitor of viral assembly (e.g.,
10 Rifampicin), or an antiviral agent that stimulates the immune system (e.g., interferons). Exemplary antiviral agents include Abacavir, Aciclovir, Acyclovir, Adefovir, Amantadine, Amprenavir, Ampligen, Arbidol, Atazanavir, Atripla (fixed dose drug), Balavir, Cidofovir, Combivir (fixed dose drug), Dolutegravir, Darunavir, Delavirdine, Didanosine, Docosanol, Edoxudine, Efavirenz, Emtricitabine, Enfuvirtide, Entecavir,
15 Ecoliever, Famciclovir, Fixed dose combination (antiretroviral), Fomivirsen, Fosamprenavir, Foscarnet, Fosfonet, Fusion inhibitor, Ganciclovir, Ibacitabine, Imunovir, Idoxuridine, lmiquimod, Indinavir, lnosine, Integrase inhibitor, Interferon type III, Interferon type II, Interferon type I, Interferon, Lamivudine, Lopinavir, Loviride, Maraviroc, Moroxydine, Methisazone, Nelfinavir, Nevirapine, Nexavir, Nitazoxanide,
20 Nucleoside analogues, Novir, Oseltamivir (Tamiflu), Peginterferon alfa-2a, Penciclovir, Peramivir, Pleconaril, Podophyllotoxin, Protease inhibitor, Raltegravir, Reverse transcriptase inhibitor, Ribavirin, Rimantadine, Ritonavir, Pyramidine, Saquinavir, Sofosbuvir, Stavudine, Synergistic enhancer (antiretroviral), Telaprevir, Tenofovir, Tenofovir disoproxil, Tipranavir, Trifluridine, Trizivir, Tromantadine, Truvada,
25 Valaciclovir (Valtrex), Valganciclovir, Vicriviroc, Vidarabine, Viramidine, Zalcitabine, Zanamivir (Relenza), and Zidovudine.

In certain embodiments, a patient diagnosed with a bacterial infection by a method described herein is administered a therapeutically effective dose of an antibiotic. Antibiotics may include broad spectrum, bactericidal, or bacteriostatic antibiotics.
30 Exemplary antibiotics include aminoglycosides such as Amikacin, Amikin, Gentamicin, Garamycin, Kanamycin, Kantrex, Neomycin, Neo-Fradin, Netilmicin, Netromycin,

Tobramycin, Nebcin, Paromomycin, Humatin, Streptomycin, Spectinomycin(Bs), and Trobicin; ansamycins such as Geldanamycin, Herbimycin, Rifaximin, and Xifaxan; carbacephems such as Loracarbef and Lorabid; carbapenems such as Ertapenem, Invanz, Doripenem, Doribax, Imipenem/Cilastatin, Primaxin, Meropenem, and Merrem;
5 cephalosporins such as Cefadroxil, Duricef, Cefazolin, Ancef, Cefalotin or Cefalothin, Keflin, Cefalexin, Keflex, Cefaclor, Distaclor, Cefamandole, Mandol, Cefoxitin, Mefoxin, Cefprozil, Cefzil, Cefuroxime, Ceftin, Zinnat, Cefixime, Cefdinir, Cefditoren, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefepime, Maxipime, Ceftaroline fosamil, Teflaro, Ceftobiprole, and
10 Zeftera; glycopeptides such as Teicoplanin, Targocid, Vancomycin, Vancocin, Telavancin, Vibativ, Dalbavancin, Dalvance, Oritavancin, and Orbactiv; lincosamides such as Clindamycin, Cleocin, Lincomycin, and Lincocin; lipopeptides such as Daptomycin and Cubicin; macrolides such as Azithromycin, Zithromax, Sumamed, Xithrone, Clarithromycin, Biaxin, Dirithromycin, Dynabac, Erythromycin, Erythocin,
15 Erythroped, Roxithromycin, Troleandomycin, Tao, Telithromycin, Ketek, Spiramycin, and Rovamycine; monobactams such as Aztreonam and Azactam; nitrofurans such as Furazolidone, Furoxone, Nitrofurantoin, Macrodantin, and Macrobid; oxazolidinones such as Linezolid, Zyvox, VRSA, Posizolid, Radezolid, and Torezolid; penicillins such as Penicillin V, Veetids (Pen-Vee-K), Piperacillin, Pipracil, Penicillin G, Pfizerpen,
20 Temocillin, Negaban, Ticarcillin, and Ticar; penicillin combinations such as Amoxicillin/clavulanate, Augmentin, Ampicillin/sulbactam, Unasyn, Piperacillin/tazobactam, Zosyn, Ticarcillin/clavulanate, and Timentin; polypeptides such as Bacitracin, Colistin, Coly-Mycin-S, and Polymyxin B; quinolones/fluoroquinolones such as Ciprofloxacin, Cipro, Ciproxin, Ciprobay, Enoxacin, Penetrex, Gatifloxacin,
25 Tequin, Gemifloxacin, Factive, Levofloxacin, Levaquin, Lomefloxacin, Maxaquin, Moxifloxacin, Avelox, Nalidixic acid, NegGram, Norfloxacin, Noroxin, Ofloxacin, Floxin, Ocuflox Trovafloxacin, Trovan, Grepafloxacin, Raxar, Sparfloxacin, Zagam, Temafloxacin, and Omniflox; sulfonamides such as Amoxicillin, Novamox, Amoxil, Ampicillin, Principen, Azlocillin, Carbenicillin, Geocillin, Cloxacillin, Tegopen,
30 Dicloxacillin, Dynapen, Flucloxacillin, Floxapen, Mezlocillin, Mezlin, Methicillin, Staphcillin, Nafcillin, Unipen, Oxacillin, Prostaphlin, Penicillin G, Pentids, Mafenide,

Sulfamylon, Sulfacetamide, Sulamyd, Bleph-10, Sulfadiazine, Micro-Sulfon, Silver sulfadiazine, Silvadene, Sulfadimethoxine Di-Methox, Albon, Sulfamethizole, Thiosulfil Forte, Sulfamethoxazole, Gantanol, Sulfanilimide, Sulfasalazine, Azulfidine, Sulfisoxazole, Gantrisin, Trimethoprim-Sulfamethoxazole (Co-trimoxazole) (TMP-
5 SMX), Bactrim, Septra, Sulfonamidochrysoidine, and Prontosil; tetracyclines such as Demeclocycline, Declomycin, Doxycycline, Vibramycin, Minocycline, Minocin, Oxytetracycline, Terramycin, Tetracycline and Sumycin, Achromycin V, and Steclin; drugs against mycobacteria such as Clofazimine, Lamprene, Dapsone, Avlosulfon, Capreomycin, Capastat, Cycloserine, Seromycin, Ethambutol, Myambutol, Ethionamide,
10 Trecator, Isoniazid, I.N.H., Pyrazinamide, Aldinamide, Rifampicin, Rifadin, Rimactane, Rifabutin, Mycobutin, Rifapentine, Priftin, and Streptomycin; others antibiotics such as Arsphenamine, Salvarsan, Chloramphenicol, Chloromycetin, Fosfomycin, Monurol, Monuril, Fusidic acid, Fucidin, Metronidazole, Flagyl, Mupirocin, Bactroban, Platensimycin, Quinupristin/Dalfopristin, Synercid, Thiamphenicol, Tigecycline, Tigacyl,
15 Tinidazole, Tindamax Fasigyn, Trimethoprim, Proloprim, and Trimpex.

B. Detecting and Measuring Biomarkers

It is understood that the biomarkers in a sample can be measured by any suitable method known in the art. Measurement of the expression level of a biomarker can be
20 direct or indirect. For example, the abundance levels of RNAs or proteins can be directly quantitated. Alternatively, the amount of a biomarker can be determined indirectly by measuring abundance levels of cDNAs, amplified RNAs or DNAs, or by measuring quantities or activities of RNAs, proteins, or other molecules (e.g., metabolites) that are indicative of the expression level of the biomarker. The methods for measuring
25 biomarkers in a sample have many applications. For example, one or more biomarkers can be measured to aid in the diagnosis of an infection, to determine the appropriate treatment for a subject, to monitor responses in a subject to treatment, or to identify therapeutic compounds that modulate expression of the biomarkers *in vivo* or *in vitro*.

Detecting Biomarker Polynucleotides

In one embodiment, the expression levels of the biomarkers are determined by measuring polynucleotide levels of the biomarkers. The levels of transcripts of specific biomarker genes can be determined from the amount of mRNA, or polynucleotides
5 derived therefrom, present in a biological sample. Polynucleotides can be detected and quantitated by a variety of methods including, but not limited to, microarray analysis, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), Northern blot, serial analysis of gene expression (SAGE), RNA switches, and solid-state nanopore detection. See, e.g., Draghici *Data Analysis Tools for DNA*
10 *Microarrays*, Chapman and Hall/CRC, 2003; Simon et al. *Design and Analysis of DNA Microarray Investigations*, Springer, 2004; *Real-Time PCR: Current Technology and Applications*, Logan, Edwards, and Saunders eds., Caister Academic Press, 2009; Bustin *A-Z of Quantitative PCR* (IUL Biotechnology, No. 5), International University Line, 2004; Velculescu et al. (1995) Science 270: 484-487; Matsumura et al. (2005) Cell.
15 Microbiol. 7: 11-18; *Serial Analysis of Gene Expression (SAGE): Methods and Protocols (Methods in Molecular Biology)*, Humana Press, 2008; herein incorporated by reference in their entireties.

In one embodiment, microarrays are used to measure the levels of biomarkers. An advantage of microarray analysis is that the expression of each of the biomarkers can
20 be measured simultaneously, and microarrays can be specifically designed to provide a diagnostic expression profile for a particular disease or condition (e.g., sepsis).

Microarrays are prepared by selecting probes which comprise a polynucleotide sequence, and then immobilizing such probes to a solid support or surface. For example, the probes may comprise DNA sequences, RNA sequences, or copolymer sequences of
25 DNA and RNA. The polynucleotide sequences of the probes may also comprise DNA and/or RNA analogues, or combinations thereof. For example, the polynucleotide sequences of the probes may be full or partial fragments of genomic DNA. The polynucleotide sequences of the probes may also be synthesized nucleotide sequences, such as synthetic oligonucleotide sequences. The probe sequences can be synthesized
30 either enzymatically *in vivo*, enzymatically *in vitro* (e.g., by PCR), or non-enzymatically *in vitro*.

Probes used in the methods of the invention are preferably immobilized to a solid support which may be either porous or non-porous. For example, the probes may be polynucleotide sequences which are attached to a nitrocellulose or nylon membrane or filter covalently at either the 3' or the 5' end of the polynucleotide. Such hybridization probes are well known in the art (see, e.g., Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001). Alternatively, the solid support or surface may be a glass, silicon, or plastic surface. In one embodiment, hybridization levels are measured to microarrays of probes consisting of a solid phase on the surface of which are immobilized a population of polynucleotides, such as a population of DNA or DNA mimics, or, alternatively, a population of RNA or RNA mimics. The solid phase may be a nonporous or, optionally, a porous material such as a gel, or a porous wafer such as a TipChip (Axela, Ontario, Canada).

In one embodiment, the microarray comprises a support or surface with an ordered array of binding (e.g., hybridization) sites or "probes" each representing one of the biomarkers described herein. Preferably the microarrays are addressable arrays, and more preferably positionally addressable arrays. More specifically, each probe of the array is preferably located at a known, predetermined position on the solid support such that the identity (i.e., the sequence) of each probe can be determined from its position in the array (i.e., on the support or surface). Each probe is preferably covalently attached to the solid support at a single site.

Microarrays can be made in a number of ways, of which several are described below. However they are produced, microarrays share certain characteristics. The arrays are reproducible, allowing multiple copies of a given array to be produced and easily compared with each other. Preferably, microarrays are made from materials that are stable under binding (e.g., nucleic acid hybridization) conditions. Microarrays are generally small, e.g., between 0.1 cm^2 and 25 cm^2; however, larger arrays may also be used, e.g., in screening arrays. Preferably, a given binding site or unique set of binding sites in the microarray will specifically bind (e.g., hybridize) to the product of a single gene in a cell (e.g., to a specific mRNA, or to a specific cDNA derived therefrom). However, in general, other related or similar sequences will cross hybridize to a given binding site.

As noted above, the "probe" to which a particular polynucleotide molecule specifically hybridizes contains a complementary polynucleotide sequence. The probes of the microarray typically consist of nucleotide sequences of no more than 1,000 nucleotides. In some embodiments, the probes of the array consist of nucleotide sequences of 10 to 1,000 nucleotides. In one embodiment, the nucleotide sequences of the probes are in the range of 10-200 nucleotides in length and are genomic sequences of one species of organism, such that a plurality of different probes is present, with sequences complementary and thus capable of hybridizing to the genome of such a species of organism, sequentially tiled across all or a portion of the genome. In other embodiments, the probes are in the range of 10-30 nucleotides in length, in the range of 10-40 nucleotides in length, in the range of 20-50 nucleotides in length, in the range of 40-80 nucleotides in length, in the range of 50-150 nucleotides in length, in the range of 80-120 nucleotides in length, or are 60 nucleotides in length.

The probes may comprise DNA or DNA "mimics" (e.g., derivatives and analogues) corresponding to a portion of an organism's genome. In another embodiment, the probes of the microarray are complementary RNA or RNA mimics. DNA mimics are polymers composed of subunits capable of specific, Watson-Crick-like hybridization with DNA, or of specific hybridization with RNA. The nucleic acids can be modified at the base moiety, at the sugar moiety, or at the phosphate backbone (e.g., phosphorothioates).

DNA can be obtained, e.g., by polymerase chain reaction (PCR) amplification of genomic DNA or cloned sequences. PCR primers are preferably chosen based on a known sequence of the genome that will result in amplification of specific fragments of genomic DNA. Computer programs that are well known in the art are useful in the design of primers with the required specificity and optimal amplification properties, such as Oligo version 5.0 (National Biosciences). Typically each probe on the microarray will be between 10 bases and 50,000 bases, usually between 20 bases and 200 bases in length. PCR methods are well known in the art, and are described, for example, in Innis et al., eds., *PCR Protocols: A Guide To Methods And Applications*, Academic Press Inc., San Diego, Calif. (1990); herein incorporated by reference in its entirety. It will be apparent to one skilled in the art that controlled robotic systems are useful for isolating and amplifying nucleic acids.

An alternative, preferred means for generating polynucleotide probes is by synthesis of synthetic polynucleotides or oligonucleotides, e.g., using N-phosphonate or phosphoramidite chemistries (Froehler et al., Nucleic Acid Res. 14:5399-5407 (1986); McBride et al., Tetrahedron Lett. 24:246-248 (1983)). Synthetic sequences are typically between about 10 and about 500 bases in length, more typically between about 20 and about 100 bases, and most preferably between about 40 and about 70 bases in length. In some embodiments, synthetic nucleic acids include non-natural bases, such as, but by no means limited to, inosine. As noted above, nucleic acid analogues may be used as binding sites for hybridization. An example of a suitable nucleic acid analogue is peptide nucleic acid (see, e.g., Egholm et al., Nature 363:566-568 (1993); U.S. Pat. No. 5,539,083).

Probes are preferably selected using an algorithm that takes into account binding energies, base composition, sequence complexity, cross-hybridization binding energies, and secondary structure. See Friend et al., International Patent Publication WO 01/05935, published Jan. 25, 2001; Hughes et al., Nat. Biotech. 19:342-7 (2001).

A skilled artisan will also appreciate that positive control probes, e.g., probes known to be complementary and hybridizable to sequences in the target polynucleotide molecules, and negative control probes, e.g., probes known to not be complementary and hybridizable to sequences in the target polynucleotide molecules, should be included on the array. In one embodiment, positive controls are synthesized along the perimeter of the array. In another embodiment, positive controls are synthesized in diagonal stripes across the array. In still another embodiment, the reverse complement for each probe is synthesized next to the position of the probe to serve as a negative control. In yet another embodiment, sequences from other species of organism are used as negative controls or as "spike-in" controls.

The probes are attached to a solid support or surface, which may be made, e.g., from glass, plastic (e.g., polypropylene, nylon), polyacrylamide, nitrocellulose, gel, silicon, or other porous or nonporous material. One method for attaching nucleic acids to a surface is by printing on glass plates, as is described generally by Schena et al, Science 270:467-470 (1995). This method is especially useful for preparing microarrays of cDNA (See also, DeRisi et al, Nature Genetics 14:457-460 (1996); Shalon et al., Genome

Res. 6:639-645 (1996); and Schena et al., Proc. Natl. Acad. Sci. U.S.A. 93:10539-11286 (1995); herein incorporated by reference in their entireties).

A second method for making microarrays produces high-density oligonucleotide arrays. Techniques are known for producing arrays containing thousands of oligonucleotides complementary to defined sequences, at defined locations on a surface using photolithographic techniques for synthesis in situ (see, Fodor et al., 1991, Science 251:767-773; Pease et al., 1994, Proc. Natl. Acad. Sci. U.S.A. 91:5022-5026; Lockhart et al., 1996, Nature Biotechnology 14:1675; U.S. Pat. Nos. 5,578,832; 5,556,752; and 5,510,270; herein incorporated by reference in their entireties) or other methods for rapid synthesis and deposition of defined oligonucleotides (Blanchard et al., Biosensors & Bioelectronics 11:687-690; herein incorporated by reference in its entirety). When these methods are used, oligonucleotides (e.g., 60-mers) of known sequence are synthesized directly on a surface such as a derivatized glass slide. Usually, the array produced is redundant, with several oligonucleotide molecules per RNA.

Other methods for making microarrays, e.g., by masking (Maskos and Southern, 1992, Nuc. Acids. Res. 20:1679-1684; herein incorporated by reference in its entirety), may also be used. In principle, any type of array, for example, dot blots on a nylon hybridization membrane (see Sambrook, et al., *Molecular Cloning: A Laboratory Manual*, 3rd Edition, 2001) could be used. However, as will be recognized by those skilled in the art, very small arrays will frequently be preferred because hybridization volumes will be smaller.

Microarrays can also be manufactured by means of an ink jet printing device for oligonucleotide synthesis, e.g., using the methods and systems described by Blanchard in U.S. Pat. No. 6,028,189; Blanchard et al., 1996, Biosensors and Bioelectronics 11:687-690; Blanchard, 1998, in Synthetic DNA Arrays in Genetic Engineering, Vol. 20, J. K. Setlow, Ed., Plenum Press, New York at pages 111-123; herein incorporated by reference in their entireties. Specifically, the oligonucleotide probes in such microarrays are synthesized in arrays, e.g., on a glass slide, by serially depositing individual nucleotide bases in "microdroplets" of a high surface tension solvent such as propylene carbonate. The microdroplets have small volumes (e.g., 100 pL or less, more preferably 50 pL or less) and are separated from each other on the microarray (e.g., by hydrophobic domains)

to form circular surface tension wells which define the locations of the array elements (i.e., the different probes). Microarrays manufactured by this ink-jet method are typically of high density, preferably having a density of at least about 2,500 different probes per 1 cm^2. The polynucleotide probes are attached to the support covalently at either the 3' or
5 the 5' end of the polynucleotide.

Biomarker polynucleotides which may be measured by microarray analysis can be expressed RNA or a nucleic acid derived therefrom (e.g., cDNA or amplified RNA derived from cDNA that incorporates an RNA polymerase promoter), including naturally occurring nucleic acid molecules, as well as synthetic nucleic acid molecules. In one
10 embodiment, the target polynucleotide molecules comprise RNA, including, but by no means limited to, total cellular RNA, poly$(A)^+$ messenger RNA (mRNA) or a fraction thereof, cytoplasmic mRNA, or RNA transcribed from cDNA (i.e., cRNA; see, e.g., Linsley & Schelter, U.S. patent application Ser. No. 09/411,074, filed Oct. 4, 1999, or U.S. Pat. No. 5,545,522, 5,891,636, or 5,716,785). Methods for preparing total and
15 poly$(A)^+$ RNA are well known in the art, and are described generally, e.g., in Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001). RNA can be extracted from a cell of interest using guanidinium thiocyanate lysis followed by CsCl centrifugation (Chirgwin et al., 1979, Biochemistry 18:5294-5299), a silica gel-based column (e.g., RNeasy (Qiagen, Valencia, Calif.) or StrataPrep (Stratagene, La Jolla,
20 Calif.)), or using phenol and chloroform, as described in Ausubel et al., eds., 1989, *Current Protocols In Molecular Biology*, Vol. III, Green Publishing Associates, Inc., John Wiley & Sons, Inc., New York, at pp. 13.12.1-13.12.5). Poly$(A)^+$ RNA can be selected, e.g., by selection with oligo-dT cellulose or, alternatively, by oligo-dT primed reverse transcription of total cellular RNA. RNA can be fragmented by methods known
25 in the art, e.g., by incubation with $ZnCl_2$, to generate fragments of RNA.

In one embodiment, total RNA, mRNA, or nucleic acids derived therefrom, are isolated from a sample taken from a patient having an infection or inflammation. Biomarker polynucleotides that are poorly expressed in particular cells may be enriched using normalization techniques (Bonaldo et al., 1996, Genome Res. 6:791-806).
30 As described above, the biomarker polynucleotides can be detectably labeled at one or more nucleotides. Any method known in the art may be used to label the target

polynucleotides. Preferably, this labeling incorporates the label uniformly along the length of the RNA, and more preferably, the labeling is carried out at a high degree of efficiency. For example, polynucleotides can be labeled by oligo-dT primed reverse transcription. Random primers (e.g., 9-mers) can be used in reverse transcription to
5 uniformly incorporate labeled nucleotides over the full length of the polynucleotides. Alternatively, random primers may be used in conjunction with PCR methods or T7 promoter-based *in vitro* transcription methods in order to amplify polynucleotides.

The detectable label may be a luminescent label. For example, fluorescent labels, bioluminescent labels, chemiluminescent labels, and colorimetric labels may be used in
10 the practice of the invention. Fluorescent labels that can be used include, but are not limited to, fluorescein, a phosphor, a rhodamine, or a polymethine dye derivative. Chemiluminescent labels that can be used include, but are not limited to, luminol. Additionally, commercially available fluorescent labels including, but not limited to, fluorescent phosphoramidites such as FluorePrime (Amersham Pharmacia, Piscataway,
15 N.J.), Fluoredite (Miilipore, Bedford, Mass.), FAM (ABI, Foster City, Calif.), and Cy3 or Cy5 (Amersham Pharmacia, Piscataway, N.J.) can be used. Alternatively, the detectable label can be a radiolabeled nucleotide.

In one embodiment, biomarker polynucleotide molecules from a patient sample are labeled differentially from the corresponding polynucleotide molecules of a reference
20 sample. The reference can comprise polynucleotide molecules from a normal biological sample (i.e., control sample, e.g., blood or PBMCs from a subject not having an infection or inflammation) or from a reference biological sample, (e.g., blood or PBMCs from a subject having a viral infection or bacterial infection).

Nucleic acid hybridization and wash conditions are chosen so that the target
25 polynucleotide molecules specifically bind or specifically hybridize to the complementary polynucleotide sequences of the array, preferably to a specific array site, wherein its complementary DNA is located. Arrays containing double-stranded probe DNA situated thereon are preferably subjected to denaturing conditions to render the DNA single-stranded prior to contacting with the target polynucleotide molecules. Arrays
30 containing single-stranded probe DNA (e.g., synthetic oligodeoxyribonucleic acids) may

need to be denatured prior to contacting with the target polynucleotide molecules, e.g., to remove hairpins or dimers which form due to self-complementary sequences.

Optimal hybridization conditions will depend on the length (e.g., oligomer versus polynucleotide greater than 200 bases) and type (e.g., RNA, or DNA) of probe and target nucleic acids. One of skill in the art will appreciate that as the oligonucleotides become shorter, it may become necessary to adjust their length to achieve a relatively uniform melting temperature for satisfactory hybridization results. General parameters for specific (i.e., stringent) hybridization conditions for nucleic acids are described in Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001), and in Ausubel et al., *Current Protocols In Molecular Biology*, vol. 2, Current Protocols Publishing, New York (1994). Typical hybridization conditions for the cDNA microarrays of Schena et al. are hybridization in 5.times.SSC plus 0.2% SDS at 65°C for four hours, followed by washes at 25°C in low stringency wash buffer (1×SSC plus 0.2% SDS), followed by 10 minutes at 25°C in higher stringency wash buffer (0.1×SSC plus 0.2% SDS) (Schena et al., Proc. Natl. Acad. Sci. U.S.A. 93:10614 (1993)). Useful hybridization conditions are also provided in, e.g., Tijessen, 1993, *Hybridization With Nucleic Acid Probes*, Elsevier Science Publishers B.V.; and Kricka, 1992, *Nonisotopic Dna Probe Techniques*, Academic Press, San Diego, Calif. Particularly preferred hybridization conditions include hybridization at a temperature at or near the mean melting temperature of the probes (e.g., within 51°C, more preferably within 21°C) in 1 M NaCl, 50 mM MES buffer (pH 6.5), 0.5% sodium sarcosine and 30% formamide.

When fluorescently labeled gene products are used, the fluorescence emissions at each site of a microarray may be, preferably, detected by scanning confocal laser microscopy. In one embodiment, a separate scan, using the appropriate excitation line, is carried out for each of the two fluorophores used. Alternatively, a laser may be used that allows simultaneous specimen illumination at wavelengths specific to the two fluorophores and emissions from the two fluorophores can be analyzed simultaneously (see Shalon et al., 1996, "A DNA microarray system for analyzing complex DNA samples using two-color fluorescent probe hybridization," Genome Research 6:639-645, which is incorporated by reference in its entirety for all purposes). Arrays can be scanned with a laser fluorescent scanner with a computer controlled X-Y stage and a microscope

objective. Sequential excitation of the two fluorophores is achieved with a multi-line, mixed gas laser and the emitted light is split by wavelength and detected with two photomultiplier tubes. Fluorescence laser scanning devices are described in Schena et al., Genome Res. 6:639-645 (1996), and in other references cited herein. Alternatively, the fiber-optic bundle described by Ferguson et al., Nature Biotech. 14:1681-1684 (1996), may be used to monitor mRNA abundance levels at a large number of sites simultaneously. Alternatively, the probes may be labeled with fluorophores and targets measured with quenchers, such that amplification is tracked by measuring decreasing signal intensity.

In certain embodiments, the invention includes a microarray comprising a plurality of probes for detection of gene expression of a set of viral response genes and a set of bacterial response genes and/or a set of sepsis response genes.

In one embodiment, the microarray comprises an oligonucleotide that hybridizes to an IFI27 polynucleotide, an oligonucleotide that hybridizes to a JUP polynucleotide, an oligonucleotide that hybridizes to a LAX1 polynucleotide, an oligonucleotide that hybridizes to a HK3 polynucleotide, an oligonucleotide that hybridizes to a TNIP1 polynucleotide, an oligonucleotide that hybridizes to a GPAA1 polynucleotide, and an oligonucleotide that hybridizes to a CTSB polynucleotide.

In another embodiment, the microarray further comprises an oligonucleotide that hybridizes to a CEACAM1 polynucleotide, an oligonucleotide that hybridizes to a ZDHHC19 polynucleotide, an oligonucleotide that hybridizes to a C9orf95 polynucleotide, an oligonucleotide that hybridizes to a GNA15 polynucleotide, an oligonucleotide that hybridizes to a BATF polynucleotide, an oligonucleotide that hybridizes to a C3AR1 polynucleotide, an oligonucleotide that hybridizes to a KIAA1370 polynucleotide, an oligonucleotide that hybridizes to a TGFBI polynucleotide, an oligonucleotide that hybridizes to a MTCH1 polynucleotide, an oligonucleotide that hybridizes to a RPGRIP1 polynucleotide, and an oligonucleotide that hybridizes to a HLA-DPB1 polynucleotide.

Polynucleotides can also be analyzed by other methods including, but not limited to, northern blotting, nuclease protection assays, RNA fingerprinting, polymerase chain reaction, ligase chain reaction, Qbeta replicase, isothermal amplification method, strand

displacement amplification, transcription based amplification systems, nuclease protection (S1 nuclease or RNAse protection assays), SAGE as well as methods disclosed in International Publication Nos. WO 88/10315 and WO 89/06700, and International Applications Nos. PCT/US87/00880 and PCT/US89/01025; herein incorporated by reference in their entireties.

A standard Northern blot assay can be used to ascertain an RNA transcript size, identify alternatively spliced RNA transcripts, and the relative amounts of mRNA in a sample, in accordance with conventional Northern hybridization techniques known to those persons of ordinary skill in the art. In Northern blots, RNA samples are first separated by size by electrophoresis in an agarose gel under denaturing conditions. The RNA is then transferred to a membrane, cross-linked, and hybridized with a labeled probe. Nonisotopic or high specific activity radiolabeled probes can be used, including random-primed, nick-translated, or PCR-generated DNA probes, *in vitro* transcribed RNA probes, and oligonucleotides. Additionally, sequences with only partial homology (e.g., cDNA from a different species or genomic DNA fragments that might contain an exon) may be used as probes. The labeled probe, e.g., a radiolabelled cDNA, either containing the full-length, single stranded DNA or a fragment of that DNA sequence may be at least 20, at least 30, at least 50, or at least 100 consecutive nucleotides in length. The probe can be labeled by any of the many different methods known to those skilled in this art. The labels most commonly employed for these studies are radioactive elements, enzymes, chemicals that fluoresce when exposed to ultraviolet light, and others. A number of fluorescent materials are known and can be utilized as labels. These include, but are not limited to, fluorescein, rhodamine, auramine, Texas Red, AMCA blue and Lucifer Yellow. A particular detecting material is anti-rabbit antibody prepared in goats and conjugated with fluorescein through an isothiocyanate. Proteins can also be labeled with a radioactive element or with an enzyme. The radioactive label can be detected by any of the currently available counting procedures. Isotopes that can be used include, but are not limited to, ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{36}Cl, ^{35}Cr, ^{57}Co, ^{58}Co, ^{59}Fe, ^{90}Y, ^{125}I, ^{131}I, and ^{186}Re. Enzyme labels are likewise useful, and can be detected by any of the presently utilized colorimetric, spectrophotometric, fluorospectrophotometric, amperometric or gasometric techniques. The enzyme is conjugated to the selected particle by reaction with bridging

molecules such as carbodiimides, diisocyanates, glutaraldehyde and the like. Any enzymes known to one of skill in the art can be utilized. Examples of such enzymes include, but are not limited to, peroxidase, beta-D-galactosidase, urease, glucose oxidase plus peroxidase and alkaline phosphatase. U.S. Pat. Nos. 3,654,090, 3,850,752, and 4,016,043 are referred to by way of example for their disclosure of alternate labeling material and methods.

Nuclease protection assays (including both ribonuclease protection assays and S1 nuclease assays) can be used to detect and quantitate specific mRNAs. In nuclease protection assays, an antisense probe (labeled with, e.g., radiolabeled or nonisotopic) hybridizes in solution to an RNA sample. Following hybridization, single-stranded, unhybridized probe and RNA are degraded by nucleases. An acrylamide gel is used to separate the remaining protected fragments. Typically, solution hybridization is more efficient than membrane-based hybridization, and it can accommodate up to 100 μg of sample RNA, compared with the 20-30 μg maximum of blot hybridizations.

The ribonuclease protection assay, which is the most common type of nuclease protection assay, requires the use of RNA probes. Oligonucleotides and other single-stranded DNA probes can only be used in assays containing S1 nuclease. The single-stranded, antisense probe must typically be completely homologous to target RNA to prevent cleavage of the probe:target hybrid by nuclease.

Serial Analysis Gene Expression (SAGE) can also be used to determine RNA abundances in a cell sample. See, e.g., Velculescu et al., 1995, Science 270:484-7; Carulli, et al., 1998, Journal of Cellular Biochemistry Supplements 30/31:286-96; herein incorporated by reference in their entireties. SAGE analysis does not require a special device for detection, and is one of the preferable analytical methods for simultaneously detecting the expression of a large number of transcription products. First, poly A^+ RNA is extracted from cells. Next, the RNA is converted into cDNA using a biotinylated oligo (dT) primer, and treated with a four-base recognizing restriction enzyme (Anchoring Enzyme: AE) resulting in AE-treated fragments containing a biotin group at their 3' terminus. Next, the AE-treated fragments are incubated with streptavidin for binding. The bound cDNA is divided into two fractions, and each fraction is then linked to a different double-stranded oligonucleotide adapter (linker) A or B. These linkers are

composed of: (1) a protruding single strand portion having a sequence complementary to the sequence of the protruding portion formed by the action of the anchoring enzyme, (2) a 5' nucleotide recognizing sequence of the IIS-type restriction enzyme (cleaves at a predetermined location no more than 20 bp away from the recognition site) serving as a tagging enzyme (TE), and (3) an additional sequence of sufficient length for constructing a PCR-specific primer. The linker-linked cDNA is cleaved using the tagging enzyme, and only the linker-linked cDNA sequence portion remains, which is present in the form of a short-strand sequence tag. Next, pools of short-strand sequence tags from the two different types of linkers are linked to each other, followed by PCR amplification using primers specific to linkers A and B. As a result, the amplification product is obtained as a mixture comprising myriad sequences of two adjacent sequence tags (ditags) bound to linkers A and B. The amplification product is treated with the anchoring enzyme, and the free ditag portions are linked into strands in a standard linkage reaction. The amplification product is then cloned. Determination of the clone's nucleotide sequence can be used to obtain a read-out of consecutive ditags of constant length. The presence of mRNA corresponding to each tag can then be identified from the nucleotide sequence of the clone and information on the sequence tags.

Quantitative reverse transcriptase PCR (qRT-PCR) can also be used to determine the expression profiles of biomarkers (see, e.g., U.S. Patent Application Publication No. 2005/0048542A1; herein incorporated by reference in its entirety). The first step in gene expression profiling by RT-PCR is the reverse transcription of the RNA template into cDNA, followed by its exponential amplification in a PCR reaction. The two most commonly used reverse transcriptases are avilo myeloblastosis virus reverse transcriptase (AMV-RT) and Moloney murine leukemia virus reverse transcriptase (MLV-RT). The reverse transcription step is typically primed using specific primers, random hexamers, or oligo-dT primers, depending on the circumstances and the goal of expression profiling. For example, extracted RNA can be reverse-transcribed using a GeneAmp RNA PCR kit (Perkin Elmer, Calif., USA), following the manufacturer's instructions. The derived cDNA can then be used as a template in the subsequent PCR reaction.

Although the PCR step can use a variety of thermostable DNA-dependent DNA polymerases, it typically employs the Taq DNA polymerase, which has a 5'-3' nuclease

activity but lacks a 3'-5' proofreading endonuclease activity. Thus, TAQMAN PCR typically utilizes the 5'-nuclease activity of Taq or Tth polymerase to hydrolyze a hybridization probe bound to its target amplicon, but any enzyme with equivalent 5' nuclease activity can be used. Two oligonucleotide primers are used to generate an amplicon typical of a PCR reaction. A third oligonucleotide, or probe, is designed to detect nucleotide sequence located between the two PCR primers. The probe is non-extendible by Taq DNA polymerase enzyme, and is labeled with a reporter fluorescent dye and a quencher fluorescent dye. Any laser-induced emission from the reporter dye is quenched by the quenching dye when the two dyes are located close together as they are on the probe. During the amplification reaction, the Taq DNA polymerase enzyme cleaves the probe in a template-dependent manner. The resultant probe fragments disassociate in solution, and signal from the released reporter dye is free from the quenching effect of the second fluorophore. One molecule of reporter dye is liberated for each new molecule synthesized, and detection of the unquenched reporter dye provides the basis for quantitative interpretation of the data.

TAQMAN RT-PCR can be performed using commercially available equipment, such as, for example, ABI PRISM 7700 sequence detection system (Perkin-Elmer-Applied Biosystems, Foster City, Calif., USA), or Lightcycler (Roche Molecular Biochemicals, Mannheim, Germany). Alternatives include, but are not limited to, sample-to-answer point-of-need devices such as cobas Liat (Roche Molecular Diagnostics, Pleasanton, Calif., USA) or GeneXpert systems (Cepheid, Sunnyvale, Calif., USA). One of ordinary skill will appreciate that the invention is not limited to the listed devices, and that other devices can be used for TAQMAN-PCR. In a preferred embodiment, the 5' nuclease procedure is run on a real-time quantitative PCR device such as the ABI PRISM 7700 sequence detection system. The system consists of a thermocycler, laser, charge-coupled device (CCD), camera and computer. The system includes software for running the instrument and for analyzing the data. 5'-Nuclease assay data are initially expressed as Ct, or the threshold cycle. Fluorescence values are recorded during every cycle and represent the amount of product amplified to that point in the amplification reaction. The point when the fluorescent signal is first recorded as statistically significant is the threshold cycle (Ct). Alternatives to standard thermal cycling include, but are not limited

to, amplification by continuous thermal gradient, or isothermal amplification with endpoint detection and other known devices to those of ordinary skill. To minimize errors and the effect of sample-to-sample variation, RT-PCR is usually performed using an internal standard. The ideal internal standard is expressed at a constant level among different tissues, and is unaffected by the experimental treatment. RNAs most frequently used to normalize patterns of gene expression are mRNAs for the housekeeping genes glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) and beta-actin.

A more recent variation of the RT-PCR technique is the real time quantitative PCR, which measures PCR product accumulation through a dual-labeled fluorigenic probe (i.e., TAQMAN probe). Real time PCR is compatible both with quantitative competitive PCR, where internal competitor for each target sequence is used for normalization, and with quantitative comparative PCR using a normalization gene contained within the sample, or a housekeeping gene for RT-PCR. For further details see, e.g. Held et al., Genome Research 6:986-994 (1996).

An alternative is the detection of PCR products using digital counting methods. These include, but are not limited to, digital droplet PCR and solid-state nanopore detection of PCR products. In these methods the counts of the products of interests may be normalized to the counts of housekeeping genes. Other methods of PCR detection known to those of ordinary skill can be used, and the invention is not limited to the listed methods.

Analysis of Biomarker Data

Biomarker data may be analyzed by a variety of methods to identify biomarkers and determine the statistical significance of differences in observed levels of biomarkers between test and reference expression profiles in order to evaluate whether a patient has inflammation arising from a noninfectious source, such as traumatic injury, surgery, autoimmune disease, thrombosis, or systemic inflammatory response syndrome (SIRS) or an infection, and if the patient is diagnosed with an infection, to diagnose the type of infection, including determining whether a patient has a viral infection or a bacterial infection. In certain embodiments, patient data is analyzed by one or more methods including, but not limited to, multivariate linear discriminant analysis (LDA), receiver

operating characteristic (ROC) analysis, principal component analysis (PCA), ensemble data mining methods, significance analysis of microarrays (SAM), cell specific significance analysis of microarrays (csSAM), spanning-tree progression analysis of density-normalized events (SPADE), and multi-dimensional protein identification
5 technology (MUDPIT) analysis. (See, e.g., Hilbe (2009) Logistic Regression Models, Chapman & Hall/CRC Press; McLachlan (2004) Discriminant Analysis and Statistical Pattern Recognition. Wiley Interscience; Zweig et al. (1993) Clin. Chem. 39:561-577; Pepe (2003) The statistical evaluation of medical tests for classification and prediction, New York, NY: Oxford; Sing et al. (2005) Bioinformatics 21:3940-3941; Tusher et al.
10 (2001) Proc. Natl. Acad. Sci. U.S.A. 98:5116-5121; Oza (2006) Ensemble data mining, NASA Ames Research Center, Moffett Field, CA, USA; English et al. (2009) J. Biomed. Inform. 42(2):287-295; Zhang (2007) Bioinformatics 8: 230; Shen-Orr et al. (2010) Journal of Immunology 184:144-130; Qiu et al. (2011) Nat. Biotechnol. 29(10):886-891; Ru et al. (2006) J. Chromatogr. A. 1111(2):166-174, Jolliffe Principal Component
15 Analysis (Springer Series in Statistics, 2nd edition, Springer, NY, 2002), Koren et al. (2004) IEEE Trans Vis Comput Graph 10:459-470; herein incorporated by reference in their entireties.)

C. Kits

20 In yet another aspect, the invention provides kits for diagnosing an infection in a subject, wherein the kits can be used to detect the biomarkers of the present invention. For example, the kits can be used to detect any one or more of the biomarkers described herein, which are differentially expressed in samples of a patient having a viral or bacterial infection and healthy or non-infected subjects. The kit may include one or more
25 agents for measuring the levels of expression of a set of viral response genes and a set of bacterial response genes, a container for holding a biological sample isolated from a human subject suspected of having an infection; and printed instructions for reacting agents with the biological sample or a portion of the biological sample for measuring the levels of expression of a set of viral response genes and a set of bacterial response genes
30 in the biological sample. The agents may be packaged in separate containers. The kit

may further comprise one or more control reference samples and reagents for performing an immunoassay, PCR, or microarray analysis.

In one embodiment, the kit comprises agents for measuring the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB biomarkers for distinguishing viral
5 infections from bacterial infections.

In another embodiment, the kit further comprises agents for measuring the levels of CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers for distinguishing whether inflammation is caused by an infectious or non-infectious source.

10 In certain embodiments, the kit further comprises a microarray for analysis of a plurality of biomarker polynucleotides. In one embodiment, the microarray comprises an oligonucleotide that hybridizes to an IFI27 polynucleotide, an oligonucleotide that hybridizes to a JUP polynucleotide, an oligonucleotide that hybridizes to a LAX1 polynucleotide, an oligonucleotide that hybridizes to a HK3 polynucleotide, an
15 oligonucleotide that hybridizes to a TNIP1 polynucleotide, an oligonucleotide that hybridizes to a GPAA1 polynucleotide, and an oligonucleotide that hybridizes to a CTSB polynucleotide

In another embodiment, the kit further comprises a microarray comprising an oligonucleotide that hybridizes to a CEACAM1 polynucleotide, an oligonucleotide that
20 hybridizes to a ZDHHC19 polynucleotide, an oligonucleotide that hybridizes to a C9orf95 polynucleotide, an oligonucleotide that hybridizes to a GNA15 polynucleotide, an oligonucleotide that hybridizes to a BATF polynucleotide, an oligonucleotide that hybridizes to a C3AR1 polynucleotide, an oligonucleotide that hybridizes to a KIAA1370 polynucleotide, an oligonucleotide that hybridizes to a TGFBI polynucleotide, an
25 oligonucleotide that hybridizes to a MTCH1 polynucleotide, an oligonucleotide that hybridizes to a RPGRIP1 polynucleotide, and an oligonucleotide that hybridizes to a HLA-DPB1 polynucleotide.

The kit can comprise one or more containers for compositions contained in the kit. Compositions can be in liquid form or can be lyophilized. Suitable containers for the
30 compositions include, for example, bottles, vials, syringes, and test tubes. Containers can be formed from a variety of materials, including glass or plastic. The kit can also

comprise a package insert containing written instructions for methods of diagnosing infections.

The kits of the invention have a number of applications. For example, the kits can be used to determine if a subject has an infection or some other inflammatory condition arising from a noninfectious source, such as traumatic injury, surgery, autoimmune disease, thrombosis, or systemic inflammatory response syndrome (SIRS). If a patient is diagnosed with an infection, the kits can be used to further determine the type of infection (i.e., viral or bacterial infection). In another example, the kits can be used to determine if a patient having acute inflammation should be treated, for example, with broad spectrum antibiotics or antiviral agents. In another example, kits can be used to monitor the effectiveness of treatment of a patient having an infection. In a further example, the kits can be used to identify compounds that modulate expression of one or more of the biomarkers in *in vitro* or *in vivo* animal models to determine the effects of treatment.

D. Diagnostic System and Computerized Methods for Diagnosis of an Infection

In a further aspect, the invention includes a computer implemented method for diagnosing a patient suspected of having an infection. The computer performs steps comprising: receiving inputted patient data comprising values for the levels of expression of either or both of a set of viral response genes and a set of bacterial response genes in a biological sample from the patient; analyzing the levels of expression of the set of genes; calculating a bacterial/viral metascore for the patient based on the levels of expression of the set of genes, wherein the value of the bacterial/viral metascore indicates whether the patient has a viral infection or a bacterial infection; and displaying information regarding the diagnosis of the patient.

In certain embodiments, the inputted patient data comprises values for the levels of expression of a set of viral response genes and a set of bacterial response genes selected from the group consisting of: a) a set of viral response genes comprising IFI27, JUP, and LAX1 and a set of bacterial response genes comprising HK3, TNIP1, GPAA1, and CTSB; b) a set of viral response genes comprising OAS2 and CUL1 and a set of bacterial response genes comprising SLC12A9, ACPP, STAT5B; c) a set of viral

response genes comprising ISG15 and CHST12 and a set of bacterial response genes comprising EMR1 and FLII; d) a set of viral response genes comprising IFIT1, SIGLEC1, and ADA and a set of bacterial response genes comprising PTAFR, NRD1, PLP2; e) a set of viral response genes comprising MX1 and a set of bacterial response
5 genes comprising DYSF, TWF2; f) a set of viral response genes comprising RSAD2 and a set of bacterial response genes comprising SORT1 and TSPO; g) a set of viral response genes comprising IFI44L, GZMB, and KCTD14 and a set of bacterial response genes comprising TBXAS1, ACAA1, and S100A12; h) a set of viral response genes comprising LY6E and a set of bacterial response genes comprising PGD and LAPTM5; i) a set of
10 viral response genes comprising IFI44, HESX1, and OASL and a set of bacterial response genes comprising NINJ2, DOK3, SORL1, and RAB31; j) a set of viral response genes comprising OAS1 and a set of bacterial response genes comprising IMPA2 and LTA4H.

In another embodiment, the invention includes a computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps
15 comprising: a) receiving inputted patient data comprising values for the levels in a biological sample from the patient of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, and CTSB biomarkers; b) analyzing the level of each of the biomarkers and comparing with respective reference value ranges for the biomarkers; c) calculating a bacterial/viral metascore for the patient based on the levels of expression of the biomarkers, wherein a
20 positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and d) displaying information regarding the diagnosis of the patient.

In certain embodiments, the inputted patient data further comprises values for the
25 levels of expression of a set of sepsis response genes comprising CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1, wherein the computer implemented method further comprises calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the
30 patient has an infection, and a sepsis metascore that is within the reference value ranges

for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition.

In another embodiment, the invention includes a computer implemented method for diagnosing a patient having inflammation, the computer performing steps comprising: a) receiving inputted patient data comprising values for the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in a biological sample from the patient; b) analyzing the levels of each of the biomarkers and comparing with respective reference value ranges for the biomarkers; c) calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition; d) calculating a bacterial/viral metascore for the patient if the sepsis score indicates that the patient has an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and displaying information regarding the diagnosis of the patient.

In a further aspect, the invention includes a diagnostic system for performing the computer implemented method, as described. A diagnostic system includes a computer containing a processor, a storage component (i.e., memory), a display component, and other components typically present in general purpose computers. The storage component stores information accessible by the processor, including instructions that may be executed by the processor and data that may be retrieved, manipulated or stored by the processor.

The storage component includes instructions for determining the diagnosis of the patient. For example, the storage component includes instructions for calculating a bacterial/viral metascore and/or sepsis metascore, as described herein (see Example 1). In addition, the storage component may further comprise instructions for performing multivariate linear discriminant analysis (LDA), receiver operating characteristic (ROC) analysis, principal component analysis (PCA), ensemble data mining methods, cell

specific significance analysis of microarrays (csSAM), or multi-dimensional protein identification technology (MUDPIT) analysis. The computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or
5 more algorithms. The display component displays information regarding the diagnosis of the patient.

The storage component may be of any type capable of storing information accessible by the processor, such as a hard-drive, memory card, ROM, RAM, DVD, CD-ROM, USB Flash drive, write-capable, and read-only memories. The processor may be
10 any well-known processor, such as processors from Intel Corporation. Alternatively, the processor may be a dedicated controller such as an ASIC.

The instructions may be any set of instructions to be executed directly (such as machine code) or indirectly (such as scripts) by the processor. In that regard, the terms "instructions," "steps" and "programs" may be used interchangeably herein. The
15 instructions may be stored in object code form for direct processing by the processor, or in any other computer language including scripts or collections of independent source code modules that are interpreted on demand or compiled in advance.

Data may be retrieved, stored or modified by the processor in accordance with the instructions. For instance, although the diagnostic system is not limited by any particular
20 data structure, the data may be stored in computer registers, in a relational database as a table having a plurality of different fields and records, XML documents, or flat files. The data may also be formatted in any computer-readable format such as, but not limited to, binary values, ASCII or Unicode. Moreover, the data may comprise any information sufficient to identify the relevant information, such as numbers, descriptive text,
25 proprietary codes, pointers, references to data stored in other memories (including other network locations) or information which is used by a function to calculate the relevant data.

In certain embodiments, the processor and storage component may comprise multiple processors and storage components that may or may not be stored within the
30 same physical housing. For example, some of the instructions and data may be stored on removable CD-ROM and others within a read-only computer chip. Some or all of the

instructions and data may be stored in a location physically remote from, yet still accessible by, the processor. Similarly, the processor may actually comprise a collection of processors which may or may not operate in parallel.

In one aspect, computer is a server communicating with one or more client computers. Each client computer may be configured similarly to the server, with a processor, storage component and instructions. Each client computer may be a personal computer, intended for use by a person, having all the internal components normally found in a personal computer such as a central processing unit (CPU), display (for example, a monitor displaying information processed by the processor), CD-ROM, hard-drive, user input device (for example, a mouse, keyboard, touch-screen or microphone), speakers, modem and/or network interface device (telephone, cable or otherwise) and all of the components used for connecting these elements to one another and permitting them to communicate (directly or indirectly) with one another. Moreover, computers in accordance with the systems and methods described herein may comprise any device capable of processing instructions and transmitting data to and from humans and other computers including network computers lacking local storage capability.

Although the client computers and may comprise a full-sized personal computer, many aspects of the system and method are particularly advantageous when used in connection with mobile devices capable of wirelessly exchanging data with a server over a network such as the Internet. For example, client computer may be a wireless-enabled PDA such as a Blackberry phone, Apple iPhone, Android, or other Internet-capable cellular phone. In such regard, the user may input information using a small keyboard, a keypad, a touch screen, or any other means of user input. The computer may have an antenna for receiving a wireless signal.

The server and client computers are capable of direct and indirect communication, such as over a network. Although only a few computers can be used, it should be appreciated that a typical system can include a large number of connected computers, with each different computer being at a different node of the network. The network, and intervening nodes, may comprise various combinations of devices and communication protocols including the Internet, World Wide Web, intranets, virtual private networks, wide area networks, local networks, cell phone networks, private networks using

communication protocols proprietary to one or more companies, Ethernet, WiFi and HTTP. Such communication may be facilitated by any device capable of transmitting data to and from other computers, such as modems (e.g., dial-up or cable), networks and wireless interfaces. The server may be a web server.

5 Although certain advantages are obtained when information is transmitted or received as noted above, other aspects of the system and method are not limited to any particular manner of transmission of information. For example, in some aspects, information may be sent via a medium such as a disk, tape, flash drive, DVD, or CD-ROM. In other aspects, the information may be transmitted in a non-electronic format

10 and manually entered into the system. Yet further, although some functions are indicated as taking place on a server and others on a client, various aspects of the system and method may be implemented by a single computer having a single processor.

III. Experimental

15 Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of

20 course, be allowed for.

Example 1

Robust Classification of Bacterial and Viral Infections Via Integrated Host Gene

25 Expression Diagnostics

Introduction

Here, we sought to improve the diagnostic power of the Sepsis MetaScore (SMS) by adding the ability to discriminate bacterial from viral infections. Thus, in order to

30 derive a new biomarker for discriminating infection types, we applied our multi-cohort analysis framework to clinical microarray cohorts that compared the host response to

bacterial and viral infections. We further developed a new method to co-normalize gene expression data among multiple cohorts, allowing direct comparison of a diagnostic score among multiple cohorts. Finally, we combined the Sepsis MetaScore and the new bacterial/viral diagnostic into an integrated antibiotic decision model (IADM) that can
5 determine whether a patient with acute inflammation from any source has an underlying bacterial infection.

Results

Derivation of the 7-gene bacterial/viral metascore

10 Our previously published 11-gene SMS cannot reliably distinguish between bacterial and viral infections, showing mostly non-significant differences in score distribution between patients with bacterial and viral infections (**FIGS. 5A and 5B**). Having previously shown that there is a conserved host gene response to viral infections[15], we hypothesized that a classifier for bacterial vs. viral infections would
15 allow for an improved diagnostic model. We thus performed a systematic search for gene expression microarray cohorts that studied patients with viral and/or bacterial infections. We identified 8 cohorts[11,18-26] (both whole blood and PBMCs) that included N > 5 patients with both viral and bacterial infections (**Table 1A**). The 8 cohorts are composed of 426 patient samples (142 viral and 284 bacterial infections), including children and
20 adults, medical and surgical patients, and with multiple sites of infection. We performed multi-cohort analysis on the 8 cohorts as previously described (**FIG. 6**)[7,15,16,27]. We set significance thresholds of an effect size >2-fold and an FDR <1% in leave-one-dataset-out round-robin analysis. However, in order to make sure that neither tissue type was biasing results, we further selected only those genes that also had an effect size >1.5 fold
25 in separate analyses of both PBMCs and whole blood cohorts. This process resulted in 72 significantly differentially expressed genes (**Supplemental Table 1**). A greedy forward search[7] was then used to find a gene set optimized for diagnosis, resulting in 7 genes (higher in viral infections: *IFI27, JUP, LAX1,* higher in bacterial infections: *HK3, TNIP1, GPAA1, CTSB;* **FIG. 7**). As expected, a 'bacterial/viral metascore' based on these 7
30 genes robustly distinguished viral from bacterial infections in all 8 of the discovery cohorts (summary ROC AUC=0.97, 95% CI=0.89-0.99, **FIG. 1A, FIG. 8**).

We next tested the 7-gene set in the 6 remaining independent clinical cohorts[13,14,28-30] that directly compared bacterial and viral infections (total 341 samples, 138 bacterial and 203 viral), and found a summary ROC AUC of 0.91 (95% CI=0.82-0.96) (**Table 1B, FIG. 1B, FIG. 9**). As a test of signature generalizability, we also tested
5 whether cells stimulated *in vitro* with LPS or influenza virus could be separated with the bacterial/viral metascore (GSE53166[31], N=75, AUC=0.99) **FIG. 10**).

Global validation via COCONUT co-normalization

There are dozens of microarray cohorts in the public domain that studied either
10 bacterial or viral infections, but not both, thus precluding a direct (within dataset) estimate of diagnostic power for separating bacterial and viral illness. In order to apply and compare a gene score across these cohorts, a new method was needed that could remove inter-dataset batch effects while remaining unbiased to the diagnosis of the diseased patients. Here we designed and implemented a new type of array normalization
15 that uses the ComBat[32] empiric Bayes normalization methods on healthy controls to obtain bias-free corrections of disease samples (a method we call COmbat CO-Normalization Using conTrols, or 'COCONUT', Methods section below, and **FIG. 11**). Importantly, housekeeping genes are invariant across both diseases and cohorts after COCONUT co-normalization, while each gene still retains the same distribution between
20 diseases and controls within each dataset (**FIGS. 12A and 12B**). Since the method assumes that all healthy samples are derived from the same distribution, we split the whole blood and PBMC samples, since different immune cell types have significantly different baseline gene expression distributions. Using COCONUT co-normalization, we were able to show that the bacterial/viral metascore has a global AUC of 0.92 (95% CI
25 0.89-0.96) in the discovery cohorts (**FIG. 2,** pre-normalized data in **FIG. 14**). We then applied this method to test the bacterial/viral metascore in all public-domain microarray cohorts that matched inclusion criteria and used whole blood (including the 4 direct validation cohorts that included control patients plus 20 cohorts that measured either bacterial or viral infections but not both[33-49], N=143+897=1,040), and showed an overall
30 ROC AUC = 0.93 (95% CI 0.91-0.94) across these data (**Table 2, FIG. 13,** pre-normalized data in **FIG. 15**). Particularly remarkable is the wide clinical variety of the

data, which include a wide range of types of infections (Gram positive, Gram negative, atypical bacterial, common respiratory viruses, and dengue) and severities (mild infections to septic shock). We were thus able to establish a single cutoff across all cohorts (shown as horizontal dotted line). Finally, we separately performed the same
5 procedure on the available PBMC validation cohorts (6 cohorts[50-54], N=259, global AUC = 0.92 (95% CI 0.87-0.97, **FIG. 16,** pre-normalized data in **FIG. 17**). Remarkably, all three global ROC AUCs using COCONUT co-normalization (discovery whole blood = 0.92, validation whole blood = 0.93, validation PBMCs = 0.92) roughly matched the summary AUC of the direct validation cohorts (0.91), giving high confidence in this level
10 of diagnostic power.

Supplemental Table 4 shows bacterial/viral metascores for all combinations of two (2) genes selected from the 71 gene set obtained by iterating the greedy forward algorithm in discovery datasets. All the 2-gene combinations from the 71 gene set show an obtained mean AUC greater than or equal to 0.80 (≥0.80). In comparison, **FIG. 18**
15 shows the distribution of mean AUCs in discovery datasets for ten thousand (10,000) randomly chosen 2-gene pairs, showing that an AUC of greater than or equal to 0.80 is not attainable by chance alone. As illustrated in **FIG. 18**, the randomly chosen 2-gene pairs result in a normal distribution of mean AUCs bounded by greater than 0.2 (>0.20) and less than 0.80 (< 0.80). The 2-gene combinations provided in Supplemental Table 4
20 with an AUC of equal or greater than 0.80 (≥0.80) have a clinically useful determination of whether an infection is viral or bacterial.

Integrated antibiotic decision model

A key clinical need is diagnosing whether a patient with signs and symptoms of
25 inflammation has an underlying bacterial infection, as rapid and judicial administration of antibiotics is key to improving patient outcomes. Neither the SMS nor the bacterial/viral metascore alone can robustly distinguish between all three classes of (1) non-infected inflammation, (2) bacterial illness and (3) viral illness. Thus, to increase clinical relevance, we tested an "integrated antibiotics decision model" (IADM), whereby we first
30 apply our previously-described SMS[7] to test for the presence of an infection, and then the samples that test positive for infection are tested with the bacterial/viral metascore (**FIG.**

3A). As above, the only way to establish test characteristics for the IADM simultaneously across cohorts is to use COCONUT co-normalization. However, we found that the SMS in COCONUT co-normalized data is strongly influenced by age, which could be due either to differences between healthy patients or infected patients, or both (**FIGS. 19A and 19B**). We thus excluded cohorts focused on infants (children < 1 year old) from the IADM, resulting in a total of 20 cohorts (N=1,057). The resulting global AUC for the SMS across the available data was 0.86 (95% CI 0.84-0.89) (**Supplemental Table 2, FIGS. 20A and 20B**). We set global thresholds for a SMS sensitivity for infection of 95% and a bacterial/viral metascore sensitivity for bacterial infection of 95%. This yielded an overall sensitivity and specificity for bacterial infections of 94.0% and 59.8%, respectively, and for viral infections 53.0% and 90.6%, respectively (**FIGS. 3A-3C**). These were largely unchanged if healthy patients were included in the non-infected class (**FIGS. 21A and 21B**). The overall positive and negative likelihood ratios for bacterial infection in the IADM are thus 2.34 (LR+) and 0.10 (LR-); a recent meta-analysis of procalcitonin showed a negative LR of 0.29 (95%CI 0.22-0.38)[55]. We plotted NPV and PPV vs. prevalence for these test characteristics; the NPV and PPV for bacterial infection at a prevalence of 15% are 98.3% and 29.2% (**FIG. 22**).

There was only one dataset (GSE63990[14]) which included non-infected SIRS patients and patients with both bacterial and viral illness but did not include healthy controls, precluding its addition to the global calculations. We thus tested the IADM with locally derived test thresholds. We found an overall bacterial infection sensitivity and specificity of 94.3% and 52.2%, respectively (**FIGS. 21A and 21B**).

NanoString Validation

Finally, we used targeted NanoString nCounter[56] gene expression assays to validate these results in independent whole blood samples from children with sepsis from the Genomics of Pediatric SIRS and Septic Shock Investigators (GPSSSI) cohort (total N=96, with 36 SIRS, 49 bacterial sepsis, and 11 viral sepsis patients, **FIGS. 4A-4E**). The GPSSSI cohort was also utilized by dataset GSE66099, but the children profiled here were never profiled via microarray and so are not part of the discovery datasets. In the NanoString validation cohort, the SMS AUC was 0.81 (AUC 0.80 in GSE66099).

Similarly, the bacterial/viral metascore AUC was 0.84 (AUC 0.83 in GSE66099). The microarray AUCs are thus preserved when tested with a targeted gene expression assay in new patients. Applying the same IADM, the sensitivity and specificity for bacterial infections were 89.7% and 70.0%, and for viral infections were 54.5% and 96.5%, respectively.

Discussion

Better diagnostics for acute infections are needed in both the inpatient and outpatient setting. In low-acuity outpatient settings, a simple diagnostic that can discriminate bacterial from viral infections may be enough to assist in appropriate antibiotic usage. In higher-acuity settings, causes of non-infectious inflammation become more important to rule out, and so a decision model for antibiotic prescriptions must include a non-infected (non-healthy) case. Thus, a reliable diagnostic needs to distinguish all three cases (non-infected inflammation, bacterial infection, and viral infection). Here, using 426 samples from 8 cohorts, we derived a set of just 7 genes that can accurately discriminate bacterial from viral infections across a very broad range of clinical conditions in independent cohorts (total 30 cohorts composed of 1,299 patients). We further demonstrate that by coupling our prior Sepsis MetaScore (to distinguish presence or absence of infection) with this new bacterial/viral metascore (to determine infection type) into a single integrated antibiotics decision model, we can determine with high accuracy which patients would benefit from antibiotics. Finally, we confirmed the diagnostic power of both the 7-gene set and the IADM in independent samples using a targeted NanoString assay, showing that the signatures retain diagnostic power when not relying on microarrays.

The IADM has a low negative likelihood ratio (0.10) and high estimated NPV, meaning it would be potentially effective as a rule-out test. Notably, a meta-analysis of procalcitonin that included 3,244 patients from 30 studies resulted in an overall estimated negative likelihood ratio of 0.29 (95%CI 0.22-0.38)[55]. Thus, the IADM negative likelihood ratio is significantly lower than the estimate for procalcitonin. Moreover, these test characteristics assume no knowledge of the patient and so are only estimates of the real-world clinical utility of such a test. History and physical, vital signs, and laboratory

values would all assist in a diagnosis as well. Even given these caveats, a recent economic decision model of screening ICU patients for hospital-acquired infections suggested that a test such as the IADM that can accurately diagnose bacterial and viral infections could be cost-effective[57]. Ultimately, only interventional trials will be able to
5 establish cost-effectiveness and clinical utility of a new diagnostic.

We validated our diagnostic in pediatric sepsis patients from the GPSSSI cohort using a NanoString assay. NanoString is highly accurate and is a useful tool for measuring the expression levels of multiple genes at once; however, it is also likely too slow for clinical application (4-6 hours per assay). Thus, although the assay confirms that
10 our gene set is robust in targeted measurements, further work will be needed to improve the turnaround time. There are multiple possibilities for an eventual commercial product based on rapid multiplexed qPCR. However, this technical hurdle is something that all gene expression infection diagnostics must overcome in order to gain clinical relevance.

Several groups have published models for diagnosing infections based on host
15 gene expression; none have yet made it into clinical practice. Most prior classifiers were either not tested in multiple independent cohorts, had too many genes to allow rapid profiling necessary for useful diagnosis, or both. For instance, Suarez et al. created a 10-gene K-nearest-neighbor classifier, but did not test it outside their published dataset (GSE60244)[13]. Tsalik et al. created a 122-probe (120 gene) classifier based on multiple
20 regression models, but in testing it in external GEO cohorts, they retrained their regression coefficients in each new dataset[14]. Such model re-training leads to a strong upward bias to these validation numbers (assuming that a final model would not be locally re-trained), or suggests that each new clinical site would have to gather a large prospective cohort to train the model prior to implementation. Other groups have made
25 gene expression classifiers for sepsis, but did not include models for discriminating viral infections[7,9,10]. Our new IADM is robust across a wide range of disease types and severities, but has a relatively lower sensitivity for viral infections. Non-gene expression biomarkers have also been used for infection diagnosis. Procalcitonin has been studied extensively in the setting of sepsis diagnosis, but cannot distinguish between non-infected
30 individuals and those with viral infections[58]. Protein-panel assays have been shown to discriminate bacterial from viral infections, but cannot discriminate patients with non-

infectious inflammation[59,60]. Thus all of these classifiers have certain strengths and weaknesses that will become more apparent with further prospective testing and direct comparison.

Although our goal in this study was to identify new biomarkers and not necessarily new biology, it is still important for a biomarker set to have biologic plausibility. Of the seven genes in the bacterial/viral metascore, six have previously been linked to infections or leukocyte activation. Both *IFI27* and *JUP* were shown in single-cohort genome-wide expression studies to be induced in response to viral infection[52,61], while *TNIP1* and *CTSB* have been shown to be important in modulating the NF-kB and necrotic responses to bacterial infection[62,63]. Finally, *LAX1* (upregulated in viral infections) is involved in activation of T-cells and B-cells[64], while *HK3* is instrumental in the neutrophil differentiation pathway[65]. Thus the role of these transcripts as biomarkers for infection type is novel but not unprecedented.

Here we relied on a new method, COCONUT, to directly compare our model across an enormous pool of one-class cohorts that would otherwise be unusable for benchmarking a new diagnostic. COCONUT assumes that all controls come from the same distribution; that is, the genes in each group of controls are reset to have the same mean and variance, with batch parameters learned empirically from gene groups. This method corrects for microarray and batch processing differences between cohorts, and so allows for the creation of a global ROC curve with a single threshold. This is a more 'real-world' measure of diagnostic power than simply reporting multiple validation ROC curves, as no single cutoff could attain the same test characteristics in the different cohorts[16]. The most important takeaways from the COCONUT-co-normalized data are that both the bacterial/viral metascore and the IADM retain diagnostic power across a very broad range of infection types and severities, with overall AUCs that are similar to the summary AUCs from head-to-head comparisons within cohorts.

Overall, we have leveraged our proven multi-cohort analysis pipeline to derive a highly robust model for improving infection diagnosis. Using a new method, we were able to validate this in dozens of independent microarray cohorts. We have also validated using a targeted NanoString assay in pediatric sepsis patients. While the IADM still needs to undergo optimization for rapid turnaround as well as a prospective interventional

trial, it seems clear that molecular profiling of the host genome will become part of the clinical toolkit in the future.

One of skill in the art will understand that alternative methods to the bacterial/viral metascore can be used to develop a classifier capable of distinguishing between bacterial and viral infections. Any method of machine learning known in the art can be used to develop the classifier. The method of developing a classifier can include ensemble algorithms that are made of a multitude of algorithms such as logistic regression, support vector machines, and decision trees such as random forests and gradient boosted decision trees. The classification can be developed using neural networks, which include a large number of nodes arranged in layers, where the output from a node in the first layer is used as the input for a node in the next layer. Alternatively, the classification can be developed using a support vector machine model, which is a representation of the examples as points in space, mapped so that the examples of the separate categories are divided by a clear gap that is as wide as possible. New examples are then mapped into the same space and predicted to belong to a category based on which side of the gap the new examples fall on. One of skill in the art will understand that any number of machine learning algorithms can be used to develop a classification capable of distinguishing between a bacterial and viral infection.

Methods

Systematic search and multi-cohort analysis

We performed a systematic search in NIH GEO and EBI ArrayExpress for public human microarray genome-wide expression studies using the search terms: bact[wildcard], vir[wildcard], infection, sepsis, SIRS, ICU, nosocomial, fever, pneumonia. Abstracts were screened to remove all studies that were either (1) non-clinical, (2) performed using tissues other than whole blood or PBMCs, or (3) compared patients that were not matched for clinical time.

All microarray data were re-normalized from raw data (when available) using standardized methods. Affymetrix arrays were renormalized using gcRMA (on arrays with perfect-match probes) or RMA. Illumina, Agilent, GE, and other commercial arrays were renormalized via normal-exponential background correction followed by quantile

normalization. Custom arrays were not renormalized. Data were log2 transformed, and a fixed-effect model was used to summarize probes to genes within each study. Within each study, cohorts assayed with different microarray types were treated as independent.

We performed multi-cohort meta-analysis as previously described[7,15,16,27]. Briefly, genes were summarized using Hedges' g, and the DerSimonian-Laird random-effects model was used for meta-analysis, followed by Benjamini-Hochberg multiple hypothesis correction[66]. Patients with bacterial infections were compared to patients with viral infections within studies, such that a positive effect size indicates a gene was more highly expressed in virus-infected patients, and a negative effect size indicates a gene was more highly expressed in bacteria-infected patients.

In order to find a set of genes highly conserved in differential expression between bacterial and viral infections, we selected all cohorts which directly compared patients with bacterial and viral infections. Patients with documented co-infections (i.e. both bacterial and viral) were removed. Cohorts were required to have >5 patients in each group to be included in meta-analysis. Both PBMCs and whole blood cohorts were included. Significant genes were those which had an effect size > 2-fold and an FDR < 1% in a leave-one-dataset-out round-robin analysis. However, in order to ensure that both tissue types were represented in the final gene set, we also performed separate meta-analyses of the PBMCs and whole blood cohorts, and removed all genes which had an effect size < 1.5-fold in either tissue type separately. The remaining genes were considered significant.

Derivation of 7-gene set

To find a set of highly diagnostic genes, the significant genes from the meta-analysis were run through a greedy forward search as previously described[7]. Briefly, this algorithm starts with zero genes and in each cycle adds one gene that best improves the AUC for diagnosis in the discovery cohorts, until a new gene cannot improve the discovery AUCs more than some threshold. The resulting genes are used to calculate a single 'bacterial/viral metascore', calculated as the geometric mean of the 'viral' response genes minus the geometric mean of the 'bacterial' response genes, times the ratio of the

number of genes in each set. The resulting continuous score can then be tested for diagnostic power using ROC curves.

Derivation of additional gene sets

5 In order to identify additional diagnostic gene sets, we implemented a recursive greedy forward search whereby, at the algorithm's conclusion, the resulting diagnostic gene set was removed from the possible set of significant genes, and the algorithm was run again. The first gene set was taken for further validation, but the other gene sets were noted to perform similarly in the discovery cohorts (Supplementary Table 3).

10

Direct validation of 7-gene set

The resulting gene set was first validated in the remaining public gene expression cohorts which directly compared bacterial to viral infections but were too small to use for the meta-analysis. Two cohorts (GSE60244[13] and GSE63990[14]) were made public after 15 our meta-analysis was completed, and so were used for validation. To show generalizability, we also examined one large *in vitro* dataset comparing LPS to influenza exposure in monocyte-derived dendritic cells, but this was not included in the summary AUC as it is not expected to come from the same distribution as the clinical studies.

20 **Summary ROC curves**

For both discovery and validation cohorts, summary ROC curves were constructed according to the method of Kester and Buntinx[67], and previously described[16]. Briefly, linear-exponential models are made of each ROC curve, and the parameters of these individual curves are summarized using a random-effects model to estimate the 25 overall summary ROC curve parameters. The alpha parameter controls AUC (in particular, distance of the line from the line of identity) and the beta parameter controls skewness of the ROC curve. Summary AUC confidence intervals are estimated from the standard error of the alpha and beta in meta-analysis.

30 **COCONUT co-normalization**

There are dozens of public microarray cohorts that profiled patients with either bacterial or viral infections, but not both. It would be advantageous to be able to compare a gene score across these cohorts, but has not previously been possible because each different microarray has widely different background measurements for each gene, and among studies using the same types of microarrays there are large batch effects. In order to make use of these data, we needed co-normalize these cohorts in such a way that (1) no bias is introduced that could influence final classification (i.e., the normalization protocol should be blind to diagnosis); (2) there should be no change to the distribution of a gene within a study, and (3) a gene should show the same distributions between studies after normalization. A method with these characteristics would allow our gene score to be calculated and compared across multiple studies, and thus allow us to broadly test its generalizability.

The ComBat empiric Bayes normalization method[32] is popular for cross-platform normalization, but crucially falls short of our desired criteria because it assumes an equal distribution across disease states. We thus developed a modified version of the ComBat method which co-normalizes control samples from different cohorts to allow for direct comparison of diseased samples from those same cohorts. We call this method COmbat CO- Normalization Using conTrols, or 'COCONUT'. COCONUT makes one strong assumption, which is that it forces control/healthy patients from different cohorts to represent the same distribution. Briefly, all cohorts are split into the healthy and diseased components. The healthy components undergo ComBat co-normalization without covariates. The ComBat estimated parameters $\hat{\alpha}$, $\hat{\beta}$, $\hat{\sigma}$, δ^*, and γ^* are obtained for each dataset for the healthy component, and then applied onto the diseased component (**FIG. 10**). This forces the diseased components of all cohorts to be from the same background distribution, but retains their relative distance from the healthy component (T-statistics within datasets are only different post-COCONUT due to floating-point math). Importantly, it also does not require any *a priori* knowledge of disease classification (i.e., bacterial or viral infection), thus meeting our prespecified criteria. This method does have the notable requirement that healthy/control patients are required to be present in a dataset in order for it to be pooled with other available data. Also, since healthy/control patients are set to be in the same distribution, it should only be used

where such an assumption is reasonable (i.e., within the same tissue type, among the same species, etc.).

The ComBat model and the COCONUT method

5 As described by Johnson et al., the ComBat model corrects for location and scale of each gene by first solving an ordinary least squares model for gene expression, and then shrinking the resulting parameters using an empiric Bayes estimator, solved iteratively[32]. Formally, each gene expression level Y_{ijg} (for gene g for sample j in batch i) is assumed to be composed of overall gene expression α_g, design matrix of sample
10 conditions X with regression coefficients β_g, additive and multiplicative batch effects γ_{ig} and δ_{ig}, and an error term ε_{ijg}:

$$Y_{ijg} = \alpha_g + X\beta_g + \gamma_{ig} + \delta_{ig}\varepsilon_{ijg}$$

Estimating parameters using ordinary least squares regression standardizes Y_{ijg} to a new term Z_{ijg} (where $\hat{\sigma}_g$ is the standard deviation of ε_{ijg}):

$$Z_{ijg} = \frac{Y_{ijg} - \hat{\alpha}_g - X\hat{\beta}_g}{\hat{\sigma}_g}$$

The standardized data are now distributed according to:

$$Z_{ijg} \sim N(\gamma_{ig}, \delta_{ig}^2), \text{ where } \gamma_{ig} \sim N(Y_i, \tau_i^2) \text{ and } \delta_{ig}^2 \sim \text{inverse gamma}(\lambda_i, \theta_i)$$

15 The inverse gamma is assumed as a standard uninformative prior. The remaining hyperparameters are estimated empirically, with the derivation and solution found in the original reference[32]. The estimated batch effects γ_{ig}^* and δ_{ig}^{2*} can then be used to adjust the standardized data to an empiric-Bayes batch-adjusted final output Y_{ijg}^*:

$$Y_{ijg}^* = \frac{\hat{\sigma}_g}{\delta_{ig}^*}(Z_{ijg} - \gamma_{ig}^*) + \hat{\alpha}_g + X\hat{\beta}_g$$

In our modified version of this method (COCONUT), all of the above is
20 performed according to the original method without modification. However, it is applied to only the healthy/control patients in each dataset (i.e. Y is a matrix of only healthy patient samples). The estimated parameters $\hat{\alpha}$, $\hat{\beta}$, $\hat{\sigma}$, δ^*, and γ^* are all taken and applied directly to a matrix D that consists only of diseased patient sample (which must be ordered in the same manner as Y):

$$E_{ikg} = \frac{D_{ikg} - \hat{\alpha}_g - X\hat{\beta}_g}{\hat{\sigma}_g}$$

$$D_{ikg}^{*} = \frac{\hat{\sigma}_g}{\delta_{ig}^{*}}\left(E_{ikg} - \gamma_{ig}^{*}\right) + \hat{\alpha}_g + X\hat{\beta}_g$$

We can thus obtain a batch-corrected version of diseased samples D*, which corrects for the differences between healthy controls, but does not change each submatrix D_i with respect to each Y_i.

5

Global ROCs

We used COCONUT co-normalization to test (1) all discovery cohorts and (2) all validation cohorts, even those containing only bacterial or only viral illness. We did this separately for the PBMCs and whole blood data, for reasons described above. After co-
10 normalization, the distributions for the individual cohorts were plotted together to allow for direct comparison. For each plot, we show (1) the distribution of scores for each dataset, (2) the normalized gene expression levels for each gene within the diagnostic test, and (3) housekeeping genes which are expected to show no difference between classes based on meta- analysis. The healthy patients have been removed from these
15 plots. However, to show that the distributions of genes between healthy and diseased patients within cohorts do not change after COCONUT co-normalization, we have also shown plots with both patient types with both target genes and housekeeping genes (**FIG. 11**). Genes with minimal effect size and minimal variance in meta-analysis were selected as housekeeping genes.

20 For each comparison, a single global ROC AUC was calculated, and a single threshold set to allow for an estimate of the real-world diagnostic performance of the tests. Thresholds for the cutoffs for bacterial versus viral infection were set to approximate a sensitivity for bacterial infection of 90%, since a bacterial infection false negative (i.e., the recommendation not to give antibiotics when antibiotics are needed)
25 can be devastating.

Integrated antibiotic decision model

The SMS can discriminate patients with severe acute infections from those with inflammation from other sources, however, it cannot distinguish between types of infection (**FIGS. 5A and 5B**). We thus tested an integrated antibiotics decision model (IADM) in which the 11-gene SMS is applied, followed by the 7-gene bacterial/viral metascore. This model thus identifies (1) whether a patient has an infection, and (2) if so, what type of infection is present (bacterial or viral). We were unable to identify enough validation cohorts with patients with non-infected inflammation that also included healthy controls, so in constructing the global ROCs both discovery and validation cohorts were used. Using the COCONUT co-normalization, global thresholds were set across all included cohorts, and these were applied to each individual dataset to test the ability of the IADM to correctly distinguish patients with non-infectious inflammation, bacterial infection, and viral infection. Healthy patients were not included as a diagnostic class as they were used in the co-normalization procedure. The IADM was also applied separately to all cohorts that had no healthy controls, but that included both (1) non-infected SIRS patients and (2) patients with both bacterial and viral infections.

Since positive and negative predictive value (PPV and NPV) are dependent on prevalence, and the prevalence of the data used here does not match the prevalence of infections in a hospital setting, we calculated PPV and NPV curves based on the sensitivity and specificity for bacterial infections attained with the integrated antibiotics decision model. Formally, NPV = specificity x (1-prevalence) / ((1-sensitivity) x prevalence + specificity x (1-prevalence)); PPV = sensitivity x prevalence / (sensitivity x prevalence + (1-specificity) x (1-prevalence)).

NanoString validation

Finally, 96 samples from independent patients (i.e., those never profiled via microarray) from the Genomics of Pediatric SIRS and Septic Shock Investigators trials[18-22] were tested using a targeted NanoString[56] digital multiplex gene quantitation assay. The 18 genes were not re-normalized to any housekeeping genes. The SMS and bacterial/viral metascore genes were both assayed, and the diagnostic performance of the IADM was calculated.

All analyses were conducted in the R statistical computing language (version 3.1.1). Code to recreate the multi-cohort meta-analysis has been previously deposited and is available at khatrilab.stanford.edu/sepsis.

Table 1. Datasets used in the discovery and direct validation of the bacterial/viral
5 metascore. CAP: community-acquired pneumonia. PICU: pediatric intensive care unit. RSV: respiratory syncytial virus. CMV: cytomegalovirus. MPV: metapneumovirus.

Accession	Author	Tissue	Platform	Demographic	Bacteria	Virii	Number Bacterial	Number Viral
A. Discovery datasets								
GSE6269	Ramilo	PBMC	GPL96	Children admitted with infection	E. coli, S. aureus, S. pneumo	Influenza	16	8
			GPL570		S. aureus, S. pneumo	Influenza	12	10
			GPL2507		S. aureus, S. pneumo	Influenza	73	18
GSE20346	Parnell	Whole Blood	GPL6947	Adults with CAP	Unknown bacterial pneumonia	Influenza	12	8
GSE40012	Parnell	Whole Blood	GPL6947	Adults with CAP	Unknown bacterial pneumonia	Influenza	36	11
GSE40396	Hu	Whole Blood	GPL10558	Febrile children in emergency department	Multiple	Adenovirus, enterovirus, rhinovirus, HHV6	8	35
GSE42026	Herbeg	Whole Blood	GPL6947	Children admitted with infection	Streptococcus and Staphylococcus spp.	Influenza, RSV	18	41
GSE66099	Wong	Whole Blood	GPL570	Septic children in PICU	Multiple	Influenza, HSV, CMV, BK, Adeno	109	11
B. Validation datasets								
GSE15297	Popper	Whole Blood	GPL8328	Febrile Children	Scarlet fever (Streptococcus)	Adenovirus	5	8
GSE25504	Smith	Whole Blood	GPL13667	Septic neonates	Multiple	Rhinovirus, CMV	11	3
			GPL6947		Multiple	CMV	26	1
GSE60244	Suarez	Whole Blood	GPL10558	Adults hospitalized with LRTI	Gram positive and atypical	Influenza, RSV, MPV	22	71
GSE63990	Tsalik	Whole	GPL571	Adults with	Multiple	Multiple	70	115

		Blood		ARI				
E-MEXP-3589	Almansa	Whole Blood	GPL10332	Adults w/COPD w/infection	Gram positive, Gram negative, atypical	Influenza, RSV, MPV	4	5

Table 2. Validation datasets that matched inclusion criteria and have a single known pathogen type (viral or bacterial). PICU: pediatric intensive care unit. RSV: respiratory syncytial virus. LRTI: lower respiratory tract infection. DHF: Dengue hemorrhagic fever. DSS: Dengue shock syndrome.

Accession	Author	Tissue	Platform	Demographic	Specific Pathogens	Number Bacterial	Number Viral
E-MEXP-3567	Irwin	Whole Blood	GPL96	Malawian children with bacterial meningitis or pneumonia	S. pneumoniae, N. meningitidis, or H. influenzae	12	0
GSE11755	Emonts	Whole Blood	GPL570	Children in PICU with meningococcal sepsis	N. meningitidis	6	0
GSE13015	Pankla	Whole Blood	GPL6106	Adults with bacterial sepsis	B. pseudomallei and others	45	0
			GPL6947			15	0
GSE22098	Berry	Whole Blood	GPL6947	Children with Gram positive infections	Staphylococcus and Streptococcus	52	0
GSE28750	Sutherland	Whole Blood	GPL570	Adults with community-acquired bacterial sepsis	Multiple bacteria	10	0
GSE29161	Thuny	Whole Blood	GPL6480	Adults with native valve infected endocarditis	Staphylococcus and Streptococcus	5	0
GSE33341	Ahn	Whole Blood	GPl571	Adults with septic bloodstream infections	S. aureus or E. coli	51	0
GSE40586	Lill	Whole Blood	GPL6244	Bacterial meningitis	Multiple bacteria	21	0
GSE42834	Bloom	Whole blood	GPL10558	Bacterial Pneumonia		19	0
GSE57065	Cazalis	Whole Blood	GPL570	Adults with bacterial septic shock	Multiple bacteria	82	0
GSE69528	Conejero	Whole Blood	GPL10558	Adults with bacterial sepsis	B. pseudomallei and others	83	0
E-MTAB-3162	van de Weg	Whole Blood	GPL570	Indonesian patients >14 years old with uncomplicated and	Dengue	0	30

				severe dengue			
GSE17156	Zaas	Whole blood	GPL571	Volunteers with viral challenge peak symptoms	Influenza, RSV, rhinovirus	0	27
GSE21802	Bermejo-Martin	Whole Blood	GPL6102	Adults with septic influenza	Influenza (H1N1)	0	12
GSE27131	Berdal	Whole Blood	GPL6244	Adults with septic influenza with mechanical ventilation	Influenza (H1N1)	0	7
GSE38900	Mejias	Whole blood	GPL10558	Children with acute LRTI	RSV	0	28
			GPL6884		Influenza, RSV, rhinovirus	0	153
GSE51808	Kwissa	Whole blood	GPL13158	Children and adults with uncomplicated dengue and DHF	Dengue	0	28
GSE68310	Zhai	Whole Blood	GPL10558	Adults with acute respiratory infections	Mostly influenza and rhinovirus	0	211
GSE16129	Ardura	PBMC	GPL6106	Children with invasive Staph infections	S. aureus	9	0
			GPL96			46	0
GSE23140	Liu	PBMC	GPL6254	Children with acute otitis media	S. pneumoniae	4	0
GSE34205	Ioannidis	PBMC	GPL570	Infants and children with acute respiratory infections	Influenza, RSV	0	79
GSE38246	Popper	PBMC	GPL15615	Nicaraguan children with uncomplicated dengue, DHF, and DSS	Dengue	0	95
GSE69606	Brand	PBMC	GPL570	Children with mild-to-severe RSV	RSV	0	26

Supplemental Table 1. List of all genes found to be significant (q<0.01, ES>2 fold overall and ES >1.5 fold in both PBMCs and whole blood separately) in multi-cohort analysis.

	summary effect size	**summary effect size std.err.**	**tau^2**	**hetero-geneity p value**	**Q**	**df**	**overall p value**	**overall FDR (q value)**	**mean discovery weighted AUC**
OAS1	1.184	0.146	0.105	0.003	21.322	7	4.56E-16	5.43E-12	0.808
IFIT1	1.422	0.203	0.192	0.007	19.389	7	2.47E-12	4.42E-09	0.826
TSPO	-1.233	0.177	0.141	0.009	18.858	7	3.42E-12	5.79E-09	0.781
SAMD9	1.063	0.155	0.072	0.121	11.416	7	7.30E-12	9.66E-09	0.752

EMR1	-1.074	0.158	0.054	0.206	9.705	7	9.39E-12	1.12E-08	0.768
ISG15	1.625	0.242	0.278	0.008	19.227	7	1.79E-11	1.93E-08	0.829
HERC5	1.361	0.207	0.178	0.032	15.336	7	4.58E-11	3.89E-08	0.794
NINJ2	-1.008	0.154	0.048	0.223	9.434	7	5.75E-11	4.67E-08	0.741
DDX60	1.303	0.200	0.159	0.042	14.565	7	6.91E-11	5.25E-08	0.797
HESX1	1.107	0.172	0.091	0.116	11.549	7	1.28E-10	8.69E-08	0.749
IFI6	1.292	0.204	0.199	0.005	20.207	7	2.28E-10	1.33E-07	0.794
MX1	1.600	0.253	0.328	0.003	21.525	7	2.63E-10	1.49E-07	0.826
OASL	1.192	0.189	0.195	0.001	25.432	7	2.73E-10	1.52E-07	0.788
LAX1	1.114	0.178	0.103	0.097	12.125	7	3.59E-10	1.86E-07	0.769
ACPP	-1.143	0.183	0.135	0.035	15.099	7	4.41E-10	2.19E-07	0.777
TBXAS1	-1.213	0.195	0.159	0.031	15.409	7	5.43E-10	2.55E-07	0.765
IFIT5	1.076	0.174	0.126	0.027	15.825	7	6.47E-10	3.00E-07	0.760
IFIT3	1.331	0.216	0.269	0.000	32.727	7	7.55E-10	3.42E-07	0.794
KCTD14	1.163	0.190	0.161	0.011	18.106	7	8.80E-10	3.83E-07	0.739
OAS2	1.379	0.230	0.346	0.000	56.480	7	1.99E-09	7.33E-07	0.830
PGD	-1.121	0.189	0.130	0.062	13.439	7	2.95E-09	1.01E-06	0.752
RTP4	1.084	0.189	0.132	0.059	13.565	7	9.15E-09	2.68E-06	0.741
PARP12	1.189	0.208	0.193	0.021	16.436	7	1.12E-08	3.13E-06	0.769
LY6E	1.479	0.260	0.363	0.001	23.586	7	1.29E-08	3.48E-06	0.818
S100A12	-1.067	0.190	0.135	0.056	13.727	7	1.81E-08	4.58E-06	0.737
ADA	1.015	0.183	0.146	0.015	17.395	7	2.79E-08	6.47E-06	0.730
IFI44L	1.727	0.311	0.568	0.000	31.320	7	2.90E-08	6.63E-06	0.823
SORT1	-1.013	0.184	0.161	0.005	20.064	7	4.00E-08	8.89E-06	0.760
IFI27	2.299	0.423	1.147	0.000	50.156	7	5.67E-08	1.16E-05	0.867
RSAD2	1.573	0.292	0.528	0.000	35.451	7	7.48E-08	1.47E-05	0.825
IFI44	1.519	0.283	0.493	0.000	37.895	7	8.24E-08	1.57E-05	0.816
OAS3	1.285	0.240	0.344	0.000	33.835	7	9.09E-08	1.69E-05	0.808
IFIH1	1.014	0.192	0.183	0.003	21.908	7	1.36E-07	2.42E-05	0.788
TNIP1	-1.023	0.194	0.152	0.040	14.735	7	1.42E-07	2.50E-05	0.749
RAB31	-1.167	0.225	0.284	0.000	31.645	7	2.27E-07	3.70E-05	0.753
SIGLEC1	1.447	0.281	0.493	0.000	38.460	7	2.59E-07	4.13E-05	0.816
SLC12A9	-1.215	0.237	0.306	0.000	27.836	7	2.87E-07	4.43E-05	0.786
JUP	1.008	0.198	0.209	0.000	26.258	7	3.66E-07	5.40E-05	0.783
STAT1	1.009	0.199	0.260	0.000	59.749	7	3.78E-07	5.51E-05	0.739
CUL1	1.060	0.212	0.225	0.004	20.680	7	5.96E-07	7.91E-05	0.753
PLP2	-1.246	0.250	0.325	0.002	22.620	7	5.99E-07	7.92E-05	0.768
IMPA2	-1.428	0.290	0.485	0.000	29.554	7	8.28E-07	0.00010168	0.778
DNMT1	1.071	0.217	0.222	0.012	18.048	7	8.34E-07	0.00010169	0.741
IFIT2	1.103	0.226	0.273	0.001	23.533	7	1.01E-06	0.00011836	0.749
GPAA1	-1.275	0.265	0.432	0.000	43.119	7	1.50E-06	0.0001581	0.775

CHST12	1.177	0.246	0.342	0.000	27.608	7	1.62E-06	0.00016794	0.772
LTA4H	-1.585	0.332	0.666	0.000	36.759	7	1.76E-06	0.00017814	0.766
RTN3	-1.045	0.221	0.307	0.000	46.192	7	2.39E-06	0.00022179	0.757
CETP	-1.132	0.242	0.333	0.000	29.766	7	2.86E-06	0.00025585	0.728
ISG20	1.214	0.262	0.411	0.000	34.693	7	3.64E-06	0.00030743	0.758
TALDO1	-1.138	0.246	0.344	0.000	30.764	7	3.66E-06	0.00030848	0.737
DHX58	1.197	0.259	0.370	0.001	24.871	7	3.94E-06	0.00032598	0.732
EIF2AK2	1.347	0.293	0.554	0.000	47.713	7	4.28E-06	0.00034864	0.796
HK3	-1.109	0.242	0.304	0.002	22.157	7	4.53E-06	0.00036318	0.748
ACAA1	-1.077	0.235	0.309	0.000	28.834	7	4.61E-06	0.00036811	0.745
XAF1	1.300	0.288	0.552	0.000	55.144	7	6.56E-06	0.0004871	0.782
GZMB	1.203	0.267	0.394	0.000	26.203	7	6.72E-06	0.00049528	0.770
CAT	-1.034	0.230	0.322	0.000	43.416	7	6.86E-06	0.00050173	0.710
DOK3	-1.035	0.233	0.295	0.001	25.110	7	9.08E-06	0.00062004	0.709
SORL1	-1.213	0.273	0.487	0.000	56.464	7	9.12E-06	0.00062162	0.777
PYGL	-1.157	0.261	0.375	0.001	25.452	7	9.46E-06	0.00064062	0.754
DYSF	-1.127	0.256	0.359	0.001	24.813	7	1.09E-05	0.00071449	0.748
TWF2	-1.081	0.248	0.326	0.002	23.101	7	1.27E-05	0.00078837	0.736
TKT	-1.155	0.266	0.434	0.000	40.903	7	1.40E-05	0.000852	0.728
CTSB	-1.080	0.249	0.403	0.000	64.209	7	1.48E-05	0.00088313	0.695
FLII	-1.159	0.271	0.461	0.000	46.721	7	1.95E-05	0.00110142	0.716
PROS1	-1.250	0.296	0.520	0.000	31.989	7	2.37E-05	0.00127457	0.708
NRD1	-1.103	0.261	0.400	0.000	31.123	7	2.40E-05	0.00128279	0.730
STAT5B	-1.013	0.240	0.343	0.000	44.775	7	2.46E-05	0.0013136	0.736
CYBRD1	-1.022	0.242	0.357	0.000	36.401	7	2.48E-05	0.00131834	0.715
PTAFR	-1.083	0.257	0.403	0.000	39.437	7	2.55E-05	0.00134828	0.727
LAPTM5	-1.010	0.243	0.341	0.000	31.034	7	3.32E-05	0.00165747	0.718

Supplemental Table 2. Datasets with non-infected inflammatory conditions used to test the IADM. Other datasets are listed in Tables 1 & 2. ICU: intensive care unit. CAP: community-acquired pneumonia. SLE: systemic lupus erythematosus.

Accession	Non-infected condition	Infected condition	Number Non-Infected	Number Infected
GSE28750	Post-surgical adults	Adults with community-acquired bacterial sepsis	11	10
GSE40012	Non-infected SIRS in adult ICU	Adults with CAP in ICU	24	47
GSE66099	Non-infected SIRS in pediatric ICU	Pediatric sepsis, severe sepsis and septic shock	30	120
E-MEXP-3589	Non-infected hospitalized patients with COPD	Hospitalized patients with COPD with respiratory infections	14	9
GSE22098	Children and adults with SLE and Still's disease	Children with Gram positive infections	141	52
GSE42834	Adults with sarcoidosis and lung cancer	Adults with bacterial pneumonia	99	19

Supplemental Table 3. Diagnostic gene sets identified by using a recursive greedy forward search algorithm.

Order in recursive forward search	positive in viral infection	positive in bacterial infection	GSE6269 gpl2507 AUC	GSE6269 gpl570 AUC	GSE6269 gpl96 AUC	GSE20346 gpl6947 AUC	GSE40012 gpl6947 AUC	GSE40396 gpl10558 AUC	GSE42026 gpl6947 AUC	GSE66099 gpl570 AUC	mean discovery AUC
1	IFI27, JUP, LAX1	HK3, TNIP1, GPAA1, CTSB	0.992	1	0.976	1	1	0.879	0.938	0.844	0.954
2	OAS2, CUL1	SLC12A9, ACPP, STAT5B	0.977	0.967	0.935	1	0.977	0.896	0.858	0.817	0.928
3	ISG15, CHST12	EMR1, FLII	0.945	0.933	0.938	1	0.949	0.9	0.858	0.796	0.915
4	IFIT1, SIGLEC1, ADA	PTAFR, NRD1, PLP2	1	1	0.944	1	0.975	0.907	0.858	0.764	0.931
5	MX1	DYSF, TWF2	1	0.925	0.916	1	0.977	0.961	0.848	0.706	0.917
6	RSAD2	SORT1, TSPO	0.961	0.942	0.947	1	0.952	0.879	0.9	0.736	0.915
7	IFI44L, GZMB, KCTD14	TBXAS1, ACAA1, S100A12	0.938	0.958	0.911	1	0.977	0.918	0.854	0.746	0.913
8	LY6E	PGD, LAPTM5	0.984	0.967	0.916	1	0.977	0.864	0.885	0.697	0.911
9	IFI44, HESX1, OASL	NINJ2, DOK3, SORL1, RAB31	0.961	0.967	0.94	1	0.957	0.889	0.851	0.742	0.913
10	OAS1	IMPA2, LTA4H	0.992	0.958	0.858	1	0.939	0.904	0.875	0.716	0.905
11	OAS3, EIF2AK2	TALDO1	0.945	0.992	0.928	0.979	0.851	0.793	0.847	0.717	0.882
12	DDX60, DNMT1	TKT	0.984	0.908	0.898	0.99	0.929	0.829	0.886	0.65	0.884
13	HERC5, IFIH1, SAMD9	PYGL, CETP, PROS1	0.961	0.925	0.925	0.958	0.902	0.811	0.85	0.678	0.876
14	IFI6	RTN3, CAT	0.938	0.983	0.913	1	0.889	0.854	0.79	0.651	0.877
15	IFIT3, IFIT5	CYBRD1	0.938	0.925	0.901	0.958	0.866	0.729	0.858	0.645	0.852
16	XAF1, ISG20, PARP12	null	0.867	0.925	0.944	0.948	0.841	0.764	0.837	0.598	0.84
17	IFIT2, DHX58, STAT1	null	0.883	0.9	0.848	0.938	0.879	0.736	0.833	0.578	0.824

Supplemental Table 4. Mean Area Under the Curve (AUC) for 2-Gene Combinations. Each 2-gene set was taken from the set of genes found by iterated greedy forward search (the pool of 71 genes). The AUC is the mean AUC across the discovery datasets. Only shown are those two-gene combinations with a mean AUC $\geq$ 0.80.

Gene 1	Gene 2	AUC	Gene 1	Gene 2	AUC	Gene 1	Gene 2	AUC	Gene 1	Gene 2	AUC	Gene 1	Gene 2	AUC
SIGLEC1	SLC12A9	0.925	STAT5B	LTA4H	0.881	EIF2AK2	NINJ2	0.864	IFIT2	PLP2	0.851	CYBRD1	PGD	0.836
IFI27	HK3	0.921	ADA	IFI44L	0.88	GZMB	IFI6	0.864	IFIT5	RSAD2	0.851	DYSF	SORL1	0.836
IFI27	S100A12	0.919	ADA	ISG15	0.88	HERC5	CAT	0.864	IFIT5	CYBRD1	0.851	FLII	TSPO	0.836
SIGLEC1	IMPA2	0.916	ADA	RSAD2	0.88	HERC5	FLII	0.864	ISG20	OAS3	0.851	IMPA2	TBXAS1	0.836
SIGLEC1	TBXAS1	0.916	DDX60	RAB31	0.88	HERC5	NRD1	0.864	ISG20	CETP	0.851	LAPTM5	S100A12	0.836
IFI27	DYSF	0.915	DDX60	STAT5B	0.88	HERC5	RTN3	0.864	JUP	SORT1	0.851	PGD	PROS1	0.836
IFI27	TNIP1	0.915	DNMT1	IFI6	0.88	HERC5	TNIP1	0.864	LAX1	TSPO	0.851	PGD	TBXAS1	0.836
SIGLEC1	ACAA1	0.914	EIF2AK2	TBXAS1	0.88	IFI44	IFI44L	0.864	LY6E	OASL	0.851	ADA	NRD1	0.835
SIGLEC1	DYSF	0.914	HERC5	SORL1	0.88	IFI44	MX1	0.864	MX1	XAF1	0.851	ADA	SORL1	0.835
IFI27	TSPO	0.913	HERC5	TBXAS1	0.88	IFI44	RSAD2	0.864	OAS1	OAS3	0.851	DNMT1	IFIT2	0.835
OAS2	SLC12A9	0.913	HESX1	LTA4H	0.88	IFI6	PROS1	0.864	OAS2	XAF1	0.851	DNMT1	CTSB	0.835
IFI27	EMR1	0.912	HESX1	SORL1	0.88	IFIH1	ISG15	0.864	PARP12	TALDO1	0.851	GZMB	STAT1	0.835
SIGLEC1	HK3	0.912	IFI44	IMPA2	0.88	IFIT2	EMR1	0.864	STAT1	TBXAS1	0.851	HERC5	SAMD9	0.835
IFI27	SLC12A9	0.911	IFI44	RAB31	0.88	IFIT2	SORL1	0.864	XAF1	GPAA1	0.851	HERC5	STAT1	0.835
IFI27	SORT1	0.911	IFI44L	DOK3	0.88	IFIT3	ACAA1	0.864	XAF1	RTN3	0.851	HESX1	IFIH1	0.835
OAS3	HK3	0.911	IFIH1	TSPO	0.88	IFIT3	LTA4H	0.864	SLC12A9	LAPTM5	0.851	IFI6	STAT1	0.835
SIGLEC1	STAT5B	0.911	IFIT5	RAB31	0.88	IFIT5	PLP2	0.864	NRD1	SLC12A9	0.851	KCTD14	SAMD9	0.835
IFIT1	HK3	0.91	IFIT5	SORL1	0.88	ISG15	OAS1	0.864	RTN3	SORL1	0.851	LAX1	HK3	0.835
SIGLEC1	EMR1	0.91	JUP	MX1	0.88	ISG20	RAB31	0.864	S100A12	TBXAS1	0.851	SAMD9	SIGLEC1	0.835
IFI27	PGD	0.909	JUP	NINJ2	0.88	ISG20	STAT5B	0.864	SLC12A9	TWF2	0.851	STAT1	GPAA1	0.835
CUL1	IFI27	0.908	JUP	STAT5B	0.88	KCTD14	TKT	0.864	TNIP1	SORL1	0.851	ACPP	PTAFR	0.835
IFI27	JUP	0.908	KCTD14	ACPP	0.88	LAX1	LTA4H	0.864	ADA	SLC12A9	0.85	CAT	DYSF	0.835
IFI27	ACAA1	0.908	KCTD14	GPAA1	0.88	PARP12	DYSF	0.864	CHST12	SAMD9	0.85	CETP	NRD1	0.835
IFI27	GPAA1	0.908	KCTD14	LTA4H	0.88	PARP12	NINJ2	0.864	CHST12	CETP	0.85	CTSB	NRD1	0.835
IFI27	NRD1	0.908	KCTD14	PLP2	0.88	PARP12	TBXAS1	0.864	CUL1	TKT	0.85	CYBRD1	S100A12	0.835
IFI27	STAT5B	0.908	KCTD14	TNIP1	0.88	SAMD9	TBXAS1	0.864	DDX60	EIF2AK2	0.85	DYSF	SLC12A9	0.835
IFIT1	DYSF	0.908	LAX1	OAS3	0.88	GPAA1	PLP2	0.864	DHX58	SIGLEC1	0.85	EMR1	PTAFR	0.835
OAS1	HK3	0.908	LAX1	SIGLEC1	0.88	LTA4H	PGD	0.864	GZMB	ACAA1	0.85	EMR1	SORT1	0.835
OAS1	SLC12A9	0.908	LY6E	LTA4H	0.88	S100A12	SLC12A9	0.864	GZMB	ACPP	0.85	FLII	GPAA1	0.835
OAS2	PTAFR	0.908	OAS3	NINJ2	0.88	ADA	IFIT5	0.863	GZMB	FLII	0.85	FLII	PLP2	0.835
OAS3	SLC12A9	0.908	OAS3	TWF2	0.88	CUL1	PLP2	0.863	GZMB	PYGL	0.85	HK3	IMPA2	0.835
SIGLEC1	FLII	0.908	OASL	RTN3	0.88	DDX60	CAT	0.863	IFIH1	RSAD2	0.85	LAPTM5	RAB31	0.835
SIGLEC1	TSPO	0.908	PARP12	STAT5B	0.88	DNMT1	OAS3	0.863	IFIT1	XAF1	0.85	LAPTM5	RTN3	0.835
CHST12	IFI27	0.907	RSAD2	PGD	0.88	GZMB	IFIT3	0.863	IFIT2	RTN3	0.85	NINJ2	RTN3	0.835

DNMT1	IFI27	0.907	RSAD2	PYGL	0.88	HERC5	ISG15	0.863	IFIT5	MX1	0.85	NRD1	PYGL	0.835
IFI27	ACPP	0.907	GPAA1	RAB31	0.88	HESX1	OAS2	0.863	ISG20	TKT	0.85	NRD1	S100A12	0.835
IFI27	CETP	0.907	GPAA1	SLC12A9	0.88	IFI44	OASL	0.863	KCTD14	XAF1	0.85	PTAFR	PLP2	0.835
IFIT1	PTAFR	0.907	LTA4H	TNIP1	0.88	IFI6	IFIT1	0.863	MX1	PARP12	0.85	PYGL	TBXAS1	0.835
ISG15	PTAFR	0.907	ADA	HERC5	0.879	IFI6	LY6E	0.863	OAS3	CYBRD1	0.85	CHST12	PROS1	0.834
MX1	DYSF	0.907	ADA	OAS3	0.879	IFIH1	LAX1	0.863	OASL	CAT	0.85	DDX60	DHX58	0.834
SIGLEC1	DOK3	0.907	CHST12	ISG15	0.879	IFIT3	JUP	0.863	OASL	CYBRD1	0.85	DNMT1	CYBRD1	0.834
IFI27	LAX1	0.906	CHST12	STAT5B	0.879	IFIT3	RTN3	0.863	PARP12	GPAA1	0.85	DNMT1	PYGL	0.834
IFI27	DOK3	0.906	GZMB	OAS3	0.879	IFIT5	LTA4H	0.863	RSAD2	XAF1	0.85	DNMT1	S100A12	0.834
IFI27	PTAFR	0.906	HERC5	TSPO	0.879	ISG15	OASL	0.863	SIGLEC1	XAF1	0.85	GZMB	RTN3	0.834
IFI27	RAB31	0.906	IFI44	LY6E	0.879	ISG20	MX1	0.863	STAT1	LTA4H	0.85	GZMB	SORT1	0.834
IFI27	SORL1	0.906	IFI44	DYSF	0.879	JUP	SORL1	0.863	ACAA1	RTN3	0.85	IFIH1	IFIT3	0.834
IFIT1	SLC12A9	0.906	IFI44	LTA4H	0.879	KCTD14	EMR1	0.863	ACPP	CAT	0.85	IFIT2	GPAA1	0.834
ISG15	SORT1	0.906	IFI44L	PGD	0.879	KCTD14	FLII	0.863	ACPP	PGD	0.85	IFIT2	LAPTM5	0.834
MX1	EMR1	0.906	IFI44L	TWF2	0.879	KCTD14	LAPTM5	0.863	ACPP	SLC12A9	0.85	IFIT3	IFIT5	0.834
MX1	HK3	0.906	IFIH1	DYSF	0.879	KCTD14	SORL1	0.863	CAT	IMPA2	0.85	IFIT3	XAF1	0.834
MX1	SLC12A9	0.906	IFIT1	JUP	0.879	KCTD14	STAT5B	0.863	CTSB	IMPA2	0.85	IFIT5	OAS1	0.834
MX1	SORL1	0.906	IFIT1	PROS1	0.879	LY6E	OAS3	0.863	EMR1	S100A12	0.85	LAX1	NINJ2	0.834
OAS2	DYSF	0.906	IFIT3	SORT1	0.879	OASL	PROS1	0.863	GPAA1	PGD	0.85	LAX1	SORT1	0.834
OAS2	TSPO	0.906	ISG15	CETP	0.879	PARP12	ACPP	0.863	NINJ2	SLC12A9	0.85	ACPP	PYGL	0.834
RSAD2	DYSF	0.906	ISG15	RTN3	0.879	SAMD9	PYGL	0.863	S100A12	TWF2	0.85	CAT	NRD1	0.834
IFI27	NINJ2	0.905	OAS3	GPAA1	0.879	CYBRD1	SLC12A9	0.863	CHST12	NINJ2	0.849	CAT	RAB31	0.834
IFI27	PROS1	0.905	OASL	PYGL	0.879	LTA4H	NRD1	0.863	CUL1	CTSB	0.849	CTSB	PGD	0.834
OAS1	DYSF	0.905	PARP12	SORL1	0.879	LTA4H	TBXAS1	0.863	CUL1	NINJ2	0.849	DYSF	EMR1	0.834
OASL	DYSF	0.905	GPAA1	RTN3	0.879	RTN3	SLC12A9	0.863	DDX60	OASL	0.849	DYSF	PROS1	0.834
RSAD2	SLC12A9	0.905	ADA	IFI6	0.878	ADA	IFIT3	0.862	DHX58	ISG15	0.849	DYSF	RTN3	0.834
SIGLEC1	ACPP	0.905	CHST12	DDX60	0.878	CHST12	LY6E	0.862	DHX58	OAS2	0.849	DYSF	S100A12	0.834
IFI27	FLII	0.904	CHST12	MX1	0.878	CHST12	NRD1	0.862	DHX58	RSAD2	0.849	EMR1	NINJ2	0.834
IFI27	LAPTM5	0.904	DDX60	LAX1	0.878	CUL1	TBXAS1	0.862	DHX58	FLII	0.849	EMR1	TWF2	0.834
IFIT1	EMR1	0.904	DHX58	PTAFR	0.878	CUL1	TWF2	0.862	DNMT1	TSPO	0.849	HK3	STAT5B	0.834
IFIT1	SORL1	0.904	DNMT1	IFIT1	0.878	DDX60	KCTD14	0.862	EIF2AK2	HERC5	0.849	HK3	TNIP1	0.834
MX1	PTAFR	0.904	GZMB	IFIT1	0.878	DHX58	PGD	0.862	EIF2AK2	IFIT3	0.849	PTAFR	PYGL	0.834
OAS2	SORL1	0.904	GZMB	MX1	0.878	DHX58	TBXAS1	0.862	GZMB	PARP12	0.849	SORL1	STAT5B	0.834
OAS3	DYSF	0.904	GZMB	RSAD2	0.878	DNMT1	SORL1	0.862	GZMB	CETP	0.849	SORT1	TNIP1	0.834
OASL	HK3	0.904	HERC5	RAB31	0.878	EIF2AK2	IFI6	0.862	HERC5	IFI6	0.849	ADA	PGD	0.833
RSAD2	HK3	0.904	IFI44	NINJ2	0.878	EIF2AK2	OAS3	0.862	HERC5	OAS3	0.849	CUL1	DHX58	0.833
SIGLEC1	SORT1	0.904	IFI44	STAT5B	0.878	HERC5	GPAA1	0.862	HESX1	NINJ2	0.849	DHX58	EIF2AK2	0.833
CHST12	GPAA1	0.903	IFI44L	FLII	0.878	HERC5	TKT	0.862	IFIT1	IFIT5	0.849	DHX58	CETP	0.833
IFI27	CTSB	0.903	IFI44L	LTA4H	0.878	HESX1	LY6E	0.862	IFIT2	TALDO1	0.849	DHX58	TALDO1	0.833
IFI27	IMPA2	0.903	IFI44L	TNIP1	0.878	IFI44L	IFIH1	0.862	IFIT5	SIGLEC1	0.849	DNMT1	EMR1	0.833
IFI27	TBXAS1	0.903	IFI6	DOK3	0.878	IFI44L	OAS1	0.862	IFIT5	CTSB	0.849	IFIT2	TWF2	0.833
IFI27	TWF2	0.903	IFI6	LAPTM5	0.878	IFI44L	OAS3	0.862	IFIT5	PGD	0.849	IFIT3	PARP12	0.833

IFIT1	SORT1	0.903	IFIH1	EMR1	0.878	IFI6	CYBRD1	0.862	IFIT5	PROS1	0.849	IFIT3	SAMD9	0.833
OAS2	ACAA1	0.903	IFIT3	ACPP	0.878	IFIT3	ISG15	0.862	JUP	OASL	0.849	IFIT5	OASL	0.833
OAS2	STAT5B	0.903	ISG15	CAT	0.878	IFIT3	PROS1	0.862	KCTD14	S100A12	0.849	LAX1	CAT	0.833
OAS3	SORT1	0.903	ISG15	TALDO1	0.878	IFIT3	PYGL	0.862	LAX1	PTAFR	0.849	OAS1	SAMD9	0.833
EIF2AK2	HK3	0.902	JUP	CTSB	0.878	IFIT3	TKT	0.862	PARP12	RSAD2	0.849	SAMD9	TKT	0.833
IFI27	MX1	0.902	KCTD14	RSAD2	0.878	IFIT5	ISG15	0.862	SAMD9	CAT	0.849	ACAA1	RAB31	0.833
IFI27	OAS2	0.902	LAX1	OASL	0.878	IFIT5	LAX1	0.862	XAF1	PYGL	0.849	DOK3	S100A12	0.833
IFI27	LTA4H	0.902	LY6E	RTN3	0.878	IFIT5	S100A12	0.862	ACPP	NRD1	0.849	DYSF	IMPA2	0.833
IFI27	PLP2	0.902	LY6E	TKT	0.878	ISG20	RSAD2	0.862	LTA4H	PTAFR	0.849	EMR1	FLII	0.833
IFIT1	RAB31	0.902	MX1	SIGLEC1	0.878	JUP	LY6E	0.862	ADA	IFIT2	0.848	IMPA2	TWF2	0.833
ISG15	EMR1	0.902	OAS3	S100A12	0.878	MX1	RSAD2	0.862	CHST12	JUP	0.848	PGD	PLP2	0.833
ISG15	SLC12A9	0.902	OASL	TWF2	0.878	OAS1	CYBRD1	0.862	CHST12	XAF1	0.848	PLP2	RAB31	0.833
MX1	TSPO	0.902	RSAD2	FLII	0.878	OAS2	RSAD2	0.862	CUL1	IFIT3	0.848	PTAFR	RTN3	0.833
OAS2	HK3	0.902	RSAD2	GPAA1	0.878	PARP12	ACAA1	0.862	CUL1	CAT	0.848	PTAFR	TSPO	0.833
OAS2	PGD	0.902	RSAD2	TALDO1	0.878	STAT1	HK3	0.862	DDX60	CYBRD1	0.848	PYGL	TSPO	0.833
RSAD2	SORT1	0.902	XAF1	DYSF	0.878	XAF1	PLP2	0.862	DHX58	LAPTM5	0.848	SORT1	TALDO1	0.833
SIGLEC1	PGD	0.902	XAF1	SORT1	0.878	ACPP	LTA4H	0.862	DNMT1	TALDO1	0.848	TALDO1	TSPO	0.833
SIGLEC1	PLP2	0.902	DDX60	IMPA2	0.877	CTSB	GPAA1	0.862	EIF2AK2	OAS1	0.848	ADA	NINJ2	0.832
SIGLEC1	PTAFR	0.902	DDX60	PTAFR	0.877	RAB31	STAT5B	0.862	GZMB	IFIH1	0.848	CHST12	GZMB	0.832
ADA	IFI27	0.901	DDX60	TBXAS1	0.877	SORL1	TSPO	0.862	GZMB	DYSF	0.848	CUL1	GZMB	0.832
EIF2AK2	DYSF	0.901	IFI44	DNMT1	0.877	ADA	SAMD9	0.861	HERC5	IFIT3	0.848	DHX58	ISG20	0.832
JUP	PGD	0.901	IFI44L	DNMT1	0.877	CHST12	EIF2AK2	0.861	IFI6	PARP12	0.848	DNMT1	PROS1	0.832
LY6E	DYSF	0.901	LAX1	HERC5	0.877	CHST12	TNIP1	0.861	IFIH1	IFIT1	0.848	HESX1	IFIT5	0.832
LY6E	TNIP1	0.901	HESX1	SORT1	0.877	CUL1	LY6E	0.861	IFIH1	LAPTM5	0.848	IFIT2	OAS1	0.832
MX1	IMPA2	0.901	IFI44L	LAPTM5	0.877	CUL1	RSAD2	0.861	IFIT2	MX1	0.848	ISG20	KCTD14	0.832
OAS2	RAB31	0.901	IFIT1	CAT	0.877	CUL1	ACPP	0.861	ISG20	DOK3	0.848	JUP	KCTD14	0.832
IFI27	ISG20	0.9	IFIT3	TBXAS1	0.877	CUL1	PTAFR	0.861	ISG20	PTAFR	0.848	OAS3	SAMD9	0.832
IFI27	OAS1	0.9	JUP	EMR1	0.877	DDX60	SIGLEC1	0.861	JUP	STAT1	0.848	OAS3	STAT1	0.832
IFI27	RSAD2	0.9	KCTD14	PGD	0.877	DNMT1	OASL	0.861	LAX1	ACAA1	0.848	SAMD9	RTN3	0.832
IFI27	TALDO1	0.9	OAS1	LAPTM5	0.877	HERC5	LY6E	0.861	LAX1	TBXAS1	0.848	ACAA1	PGD	0.832
IFI44	SLC12A9	0.9	OAS1	RTN3	0.877	HESX1	OAS3	0.861	LAX1	TKT	0.848	CAT	CETP	0.832
ISG15	HK3	0.9	OASL	TALDO1	0.877	HESX1	NRD1	0.861	LY6E	PARP12	0.848	CAT	RTN3	0.832
LY6E	SLC12A9	0.9	XAF1	EMR1	0.877	IFI44	IFIT1	0.861	OAS2	SAMD9	0.848	CETP	S100A12	0.832
MX1	DOK3	0.9	XAF1	PTAFR	0.877	IFI6	ISG20	0.861	PARP12	CETP	0.848	CTSB	HK3	0.832
MX1	PGD	0.9	LTA4H	EMR1	0.877	IFI6	CAT	0.861	STAT1	ACPP	0.848	CYBRD1	DOK3	0.832
OAS3	EMR1	0.9	CHST12	IFI44	0.876	IFIH1	TALDO1	0.861	ACPP	LAPTM5	0.848	DOK3	RTN3	0.832
RSAD2	SORL1	0.9	CUL1	ACAA1	0.876	IFIT3	TWF2	0.861	ACPP	PLP2	0.848	DYSF	PLP2	0.832
SIGLEC1	TWF2	0.9	DHX58	SORL1	0.876	ISG20	SORL1	0.861	CAT	LTA4H	0.848	DYSF	RAB31	0.832
GZMB	IFI27	0.899	EIF2AK2	CTSB	0.876	JUP	OAS2	0.861	CETP	GPAA1	0.848	DYSF	STAT5B	0.832
IFI27	IFI44	0.899	EIF2AK2	RTN3	0.876	KCTD14	HK3	0.861	CYBRD1	EMR1	0.848	DYSF	TSPO	0.832
IFI27	CYBRD1	0.899	HESX1	ISG15	0.876	KCTD14	TWF2	0.861	PLP2	NRD1	0.848	FLII	NINJ2	0.832

IFI27	RTN3	0.899	HESX1	EMR1	0.876	LY6E	CYBRD1	0.861	PROS1	STAT5B	0.848	FLII	RTN3	0.832
ISG15	DYSF	0.899	HESX1	PLP2	0.876	OAS3	RSAD2	0.861	S100A12	TNIP1	0.848	FLII	SORT1	0.832
JUP	TSPO	0.899	IFI44	KCTD14	0.876	OAS3	CAT	0.861	SLC12A9	TALDO1	0.848	FLII	STAT5B	0.832
LY6E	HK3	0.899	IFI44	DOK3	0.876	OAS3	PROS1	0.861	SLC12A9	TBXAS1	0.848	HK3	PLP2	0.832
LY6E	PGD	0.899	IFI44	TNIP1	0.876	SAMD9	STAT5B	0.861	SLC12A9	TKT	0.848	LAPTM5	TSPO	0.832
OAS1	IMPA2	0.899	IFI44L	KCTD14	0.876	STAT1	SLC12A9	0.861	STAT5B	TALDO1	0.848	NINJ2	RAB31	0.832
OAS1	TSPO	0.899	IFI44L	LY6E	0.876	XAF1	IMPA2	0.861	STAT5B	TKT	0.848	NINJ2	S100A12	0.832
OAS2	IMPA2	0.899	IFI6	LTA4H	0.876	GPAA1	CAT	0.861	ADA	TNIP1	0.847	PGD	SORT1	0.832
RSAD2	EMR1	0.899	IFI6	STAT5B	0.876	GPAA1	CYBRD1	0.861	DHX58	CHST12	0.847	PTAFR	PROS1	0.832
EIF2AK2	SLC12A9	0.898	IFIT1	KCTD14	0.876	EMR1	GPAA1	0.861	CHST12	TALDO1	0.847	PTAFR	SORL1	0.832
IFIT1	IFI27	0.898	IFIT1	GPAA1	0.876	GPAA1	TKT	0.861	CUL1	EMR1	0.847	RTN3	TWF2	0.832
ISG15	IFI27	0.898	JUP	LAPTM5	0.876	IMPA2	LTA4H	0.861	IFI44	DDX60	0.847	STAT1	ADA	0.831
SIGLEC1	IFI27	0.898	JUP	TKT	0.876	SLC12A9	SORL1	0.861	IFI6	DDX60	0.847	ADA	PLP2	0.831
IFI27	PYGL	0.898	KCTD14	ACAA1	0.876	STAT5B	TBXAS1	0.861	JUP	DHX58	0.847	ISG20	CHST12	0.831
IFI44	HK3	0.898	LY6E	LAX1	0.876	IFIT3	CHST12	0.86	IFIT5	DNMT1	0.847	IFIT5	DDX60	0.831
IFIT1	DOK3	0.898	SAMD9	LAX1	0.876	OASL	CHST12	0.86	DNMT1	CETP	0.847	ISG20	DNMT1	0.831
IFIT1	IMPA2	0.898	LY6E	CETP	0.876	CUL1	NRD1	0.86	OASL	HERC5	0.847	DNMT1	LAPTM5	0.831
JUP	IMPA2	0.898	OASL	CTSB	0.876	DDX60	CTSB	0.86	HESX1	CAT	0.847	SAMD9	LAPTM5	0.831
LY6E	TSPO	0.898	OASL	SORL1	0.876	DDX60	TALDO1	0.86	IFIH1	IFI44	0.847	ACAA1	PROS1	0.831
MX1	ACPP	0.898	XAF1	HK3	0.876	DDX60	TWF2	0.86	XAF1	IFI44	0.847	ACPP	EMR1	0.831
MX1	SORT1	0.898	XAF1	SORL1	0.876	DHX58	LAX1	0.86	XAF1	IFI6	0.847	CETP	TSPO	0.831
MX1	STAT5B	0.898	IFIT1	CHST12	0.875	DHX58	ACPP	0.86	IFIT2	DOK3	0.847	CYBRD1	FLII	0.831
OAS2	DOK3	0.898	IFI44L	CUL1	0.875	DHX58	RAB31	0.86	OAS2	IFIT5	0.847	EMR1	LAPTM5	0.831
OAS2	GPAA1	0.898	DDX60	ACAA1	0.875	LY6E	DNMT1	0.86	IFIT5	TNIP1	0.847	HK3	TBXAS1	0.831
OAS3	SORL1	0.898	EIF2AK2	LTA4H	0.875	SIGLEC1	DNMT1	0.86	LAX1	LAPTM5	0.847	NINJ2	NRD1	0.831
OASL	PGD	0.898	HERC5	S100A12	0.875	HERC5	CYBRD1	0.86	LAX1	NRD1	0.847	NINJ2	PYGL	0.831
OASL	PTAFR	0.898	HESX1	TBXAS1	0.875	HESX1	TWF2	0.86	SAMD9	MX1	0.847	PGD	S100A12	0.831
SIGLEC1	SORL1	0.898	HESX1	TSPO	0.875	MX1	IFIH1	0.86	STAT1	MX1	0.847	PLP2	TKT	0.831
SIGLEC1	TALDO1	0.898	IFI44	CTSB	0.875	IFIH1	FLII	0.86	PARP12	SIGLEC1	0.847	RTN3	RAB31	0.831
IFI27	LY6E	0.897	IFI44	GPAA1	0.875	IFIH1	RTN3	0.86	SAMD9	CTSB	0.847	ADA	DYSF	0.83
IFI27	OAS3	0.897	ISG15	IFI44L	0.875	IFIH1	TKT	0.86	SAMD9	DOK3	0.847	ADA	HK3	0.83
ISG15	TSPO	0.897	SIGLEC1	IFI44L	0.875	IFIH1	TWF2	0.86	ACPP	TSPO	0.847	STAT1	CHST12	0.83
LY6E	EMR1	0.897	IFI6	SORL1	0.875	IFIT3	IFIT1	0.86	CYBRD1	IMPA2	0.847	IFIH1	CUL1	0.83
LY6E	TBXAS1	0.897	MX1	ISG15	0.875	IFIT2	IMPA2	0.86	PGD	EMR1	0.847	KCTD14	DHX58	0.83
MX1	RAB31	0.897	ISG20	SLC12A9	0.875	LY6E	IFIT3	0.86	PYGL	EMR1	0.847	DNMT1	RTN3	0.83
OAS2	ACPP	0.897	KCTD14	TSPO	0.875	MX1	IFIT3	0.86	GPAA1	PROS1	0.847	IFIT2	HERC5	0.83
OAS2	NRD1	0.897	LY6E	PYGL	0.875	IFIT3	CTSB	0.86	IMPA2	SORT1	0.847	ISG20	IFIH1	0.83
OAS2	TNIP1	0.897	OAS2	CAT	0.875	IFIT3	NRD1	0.86	LAPTM5	NRD1	0.847	IFIT2	TNIP1	0.83
OAS3	TBXAS1	0.897	OASL	STAT5B	0.875	IFIT5	DYSF	0.86	PLP2	RTN3	0.847	LAX1	CYBRD1	0.83
OASL	SORT1	0.897	PARP12	PTAFR	0.875	ISG20	ACAA1	0.86	PROS1	SORL1	0.847	LAX1	RTN3	0.83
OASL	TSPO	0.897	RSAD2	PROS1	0.875	ISG20	NINJ2	0.86	RAB31	TBXAS1	0.847	SAMD9	OASL	0.83
SIGLEC1	LAPTM5	0.897	RSAD2	RTN3	0.875	LAX1	JUP	0.86	S100A12	TSPO	0.847	XAF1	PARP12	0.83

EIF2AK2	IFI27	0.896	ACPP	GPAA1	0.875	LAX1	TNIP1	0.86	JUP	ADA	0.846	STAT1	DOK3	0.83
EIF2AK2	SORT1	0.896	CHST12	IFI44L	0.874	OAS1	LY6E	0.86	ADA	IMPA2	0.846	STAT1	NRD1	0.83
EIF2AK2	STAT5B	0.896	CHST12	TWF2	0.874	SIGLEC1	OAS1	0.86	ADA	TBXAS1	0.846	STAT1	PROS1	0.83
EIF2AK2	TSPO	0.896	CUL1	TSPO	0.874	RSAD2	OASL	0.86	ADA	TSPO	0.846	ACAA1	DYSF	0.83
HESX1	IFI27	0.896	JUP	DDX60	0.874	SAMD9	DYSF	0.86	KCTD14	CHST12	0.846	ACAA1	S100A12	0.83
IFIT2	IFI27	0.896	DDX60	DYSF	0.874	SIGLEC1	CAT	0.86	CHST12	CAT	0.846	CAT	HK3	0.83
KCTD14	IFI27	0.896	DDX60	LTA4H	0.874	SIGLEC1	PROS1	0.86	CHST12	RTN3	0.846	CAT	LAPTM5	0.83
PARP12	IFI27	0.896	DHX58	TSPO	0.874	XAF1	NINJ2	0.86	OAS1	CUL1	0.846	CETP	CTSB	0.83
IFI27	STAT1	0.896	EIF2AK2	NRD1	0.874	XAF1	NRD1	0.86	OASL	CUL1	0.846	CETP	DYSF	0.83
IFI6	SORT1	0.896	HERC5	IMPA2	0.874	XAF1	TBXAS1	0.86	CUL1	PYGL	0.846	CETP	IMPA2	0.83
IFIT1	ACPP	0.896	HERC5	STAT5B	0.874	ACAA1	GPAA1	0.86	ISG20	DDX60	0.846	CTSB	TBXAS1	0.83
IFIT1	TSPO	0.896	HESX1	ACPP	0.874	ACPP	PROS1	0.86	OAS1	DDX60	0.846	CTSB	TWF2	0.83
ISG15	PGD	0.896	IFI44	PLP2	0.874	ACPP	SORL1	0.86	IFIH1	DNMT1	0.846	CYBRD1	TBXAS1	0.83
ISG15	SORL1	0.896	IFI44	S100A12	0.874	CAT	SLC12A9	0.86	DNMT1	NRD1	0.846	CYBRD1	TWF2	0.83
LY6E	PTAFR	0.896	IFI44	TWF2	0.874	EMR1	SORL1	0.86	IFIH1	EIF2AK2	0.846	IMPA2	FLII	0.83
OAS1	SORT1	0.896	IFI44L	RTN3	0.874	HK3	LTA4H	0.86	GZMB	TNIP1	0.846	HK3	NRD1	0.83
OAS1	TBXAS1	0.896	IFI44L	TALDO1	0.874	MPA2	I NRD1	0.86	OAS1	HERC5	0.846	HK3	PROS1	0.83
OAS2	EMR1	0.896	IFI44L	TKT	0.874	LTA4H	NINJ2	0.86	JUP	HESX1	0.846	HK3	SLC12A9	0.83
OAS2	LTA4H	0.896	IFI6	ISG15	0.874	LTA4H	TWF2	0.86	PARP12	IFIT1	0.846	HK3	TWF2	0.83
OAS2	TBXAS1	0.896	IFI6	SIGLEC1	0.874	NRD1	TSPO	0.86	STAT1	IFIT1	0.846	IMPA2	PROS1	0.83
OAS3	TSPO	0.896	IFI6	CTSB	0.874	RTN3	STAT5B	0.86	ISG20	RTN3	0.846	IMPA2	PTAFR	0.83
OASL	EMR1	0.896	IFIH1	ACAA1	0.874	SLC12A9	TSPO	0.86	ISG20	S100A12	0.846	IMPA2	TALDO1	0.83
OASL	SLC12A9	0.896	IFIH1	SORL1	0.874	CHST12	HK3	0.859	LAX1	PLP2	0.846	PYGL	TWF2	0.83
SIGLEC1	GPAA1	0.896	IFIT1	CETP	0.874	HERC5	CUL1	0.859	SAMD9	RSAD2	0.846	RAB31	S100A12	0.83
IFI27	HERC5	0.895	IFIT3	IMPA2	0.874	CUL1	RAB31	0.859	SAMD9	PROS1	0.846	SORT1	TKT	0.83
HESX1	SLC12A9	0.895	IFIT3	NINJ2	0.874	KCTD14	EIF2AK2	0.859	STAT1	ACAA1	0.846	SORT1	TWF2	0.83
IFI6	HK3	0.895	IFIT5	SORT1	0.874	KCTD14	HERC5	0.859	STAT1	PYGL	0.846	ADA	CYBRD1	0.829
IFIT1	NINJ2	0.895	LY6E	ISG15	0.874	HERC5	CETP	0.859	ACAA1	NRD1	0.846	LAX1	CUL1	0.829
IFIT1	TBXAS1	0.895	ISG15	CYBRD1	0.874	RSAD2	HESX1	0.859	ACAA1	STAT5B	0.846	OASL	DHX58	0.829
ISG15	ACPP	0.895	KCTD14	RTN3	0.874	HESX1	TALDO1	0.859	CETP	SORL1	0.846	DHX58	CAT	0.829
MX1	NRD1	0.895	OAS1	LAX1	0.874	HESX1	TKT	0.859	IMPA2	TNIP1	0.846	IFIT2	EIF2AK2	0.829
MX1	PLP2	0.895	LY6E	NRD1	0.874	IFI6	IFI44	0.859	LTA4H	TKT	0.846	KCTD14	IFIH1	0.829
MX1	TBXAS1	0.895	MX1	CAT	0.874	OAS3	IFI44	0.859	NRD1	PGD	0.846	STAT1	RTN3	0.829
OAS2	FLII	0.895	OAS3	NRD1	0.874	STAT1	IFI44L	0.859	NRD1	RTN3	0.846	ACAA1	PLP2	0.829
OAS2	PLP2	0.895	OAS3	TKT	0.874	IFIH1	PGD	0.859	PGD	SLC12A9	0.846	CAT	TWF2	0.829
OAS3	IMPA2	0.895	OASL	FLII	0.874	IFIT2	NINJ2	0.859	PGD	STAT5B	0.846	CETP	RTN3	0.829
OAS3	PTAFR	0.895	RSAD2	CETP	0.874	IFIT2	RAB31	0.859	SLC12A9	SORT1	0.846	CTSB	CYBRD1	0.829
IFI27	DDX60	0.894	GPAA1	S100A12	0.874	IFIT2	TBXAS1	0.859	ADA	ACPP	0.845	CTSB	PYGL	0.829
EIF2AK2	IMPA2	0.894	LTA4H	SORL1	0.874	IFIT2	TSPO	0.859	CUL1	S100A12	0.845	IMPA2	TKT	0.829
EIF2AK2	SORL1	0.894	ADA	OASL	0.873	IFIT3	KCTD14	0.859	DNMT1	DHX58	0.845	NRD1	TALDO1	0.829
IFIH1	IFI27	0.894	ADA	SIGLEC1	0.873	IFIT3	FLII	0.859	DHX58	S100A12	0.845	PLP2	TNIP1	0.829
IFI27	TKT	0.894	CHST12	IMPA2	0.873	IFIT3	LAPTM5	0.859	DNMT1	CAT	0.845	TKT	TSPO	0.829

IFI44L	PTAFR	0.894	DDX60	DOK3	0.873	PARP12	ISG15	0.859	GZMB	CAT	0.845	ISG20	ADA	0.828
IFIT1	ACAA1	0.894	DNMT1	GPAA1	0.873	SAMD9	ISG15	0.859	GZMB	EMR1	0.845	ADA	CAT	0.828
LAX1	ISG15	0.894	HERC5	GZMB	0.873	ISG20	PGD	0.859	GZMB	PTAFR	0.845	ADA	PROS1	0.828
ISG15	DOK3	0.894	HERC5	PLP2	0.873	JUP	PROS1	0.859	IFIT3	HESX1	0.845	SAMD9	DDX60	0.828
ISG15	STAT5B	0.894	ISG15	IFI44	0.873	XAF1	LAX1	0.859	SIGLEC1	HESX1	0.845	IFIT5	DHX58	0.828
OAS1	RAB31	0.894	IFI44	CAT	0.873	XAF1	LY6E	0.859	JUP	IFIH1	0.845	XAF1	DHX58	0.828
OAS2	NINJ2	0.894	IFI44	NRD1	0.873	OAS3	MX1	0.859	ISG15	IFIT2	0.845	STAT1	DNMT1	0.828
OAS2	SORT1	0.894	OAS2	IFI44L	0.873	PARP12	PGD	0.859	IFIT2	PROS1	0.845	ISG20	GZMB	0.828
OAS3	STAT5B	0.894	IFI44L	CETP	0.873	SAMD9	LTA4H	0.859	IFIT5	TALDO1	0.845	LAX1	GZMB	0.828
SIGLEC1	CTSB	0.894	IFI44L	GPAA1	0.873	XAF1	ACAA1	0.859	IFIT5	TKT	0.845	KCTD14	HESX1	0.828
DDX60	SORT1	0.893	IFIH1	ACPP	0.873	IMPA2	STAT5B	0.859	OAS1	ISG20	0.845	OASL	IFIT2	0.828
EIF2AK2	PGD	0.893	IFIT1	CYBRD1	0.873	LTA4H	RTN3	0.859	ISG20	CTSB	0.845	LAX1	ISG20	0.828
EIF2AK2	PLP2	0.893	IFIT2	HK3	0.873	PROS1	SLC12A9	0.859	JUP	CYBRD1	0.845	PARP12	ISG20	0.828
IFI44L	IFI27	0.893	IFIT5	ACPP	0.873	S100A12	SORT1	0.859	KCTD14	CAT	0.845	SAMD9	ISG20	0.828
IFI6	IFI27	0.893	IFIT5	SLC12A9	0.873	SORL1	TBXAS1	0.859	LAX1	ACPP	0.845	STAT1	KCTD14	0.828
OASL	IFI27	0.893	L AX1	KCTD14	0.873	SORL1	TWF2	0.859	LAX1	EMR1	0.845	STAT1	OAS1	0.828
IFI27	CAT	0.893	MX1	KCTD14	0.873	HESX1	ADA	0.858	OASL	OAS3	0.845	STAT1	CAT	0.828
IFI44L	EMR1	0.893	XAF1	STAT5B	0.873	XAF1	ADA	0.858	PARP12	CYBRD1	0.845	ACAA1	EMR1	0.828
IFI44L	SLC12A9	0.893	LTA4H	TSPO	0.873	HESX1	CHST12	0.858	SAMD9	CYBRD1	0.845	ACPP	DOK3	0.828
IFI6	EMR1	0.893	DDX60	ADA	0.872	IFI6	CUL1	0.858	STAT1	S100A12	0.845	CAT	PTAFR	0.828
IFI6	TSPO	0.893	OAS2	ADA	0.872	DDX60	GPAA1	0.858	CYBRD1	SORT1	0.845	CTSB	NINJ2	0.828
IFIT1	STAT5B	0.893	ADA	GPAA1	0.872	DDX60	LAPTM5	0.858	EMR1	RAB31	0.845	CTSB	S100A12	0.828
ISG15	TNIP1	0.893	RSAD2	CHST12	0.872	DDX60	PROS1	0.858	NRD1	TWF2	0.845	CTSB	TALDO1	0.828
MX1	ACAA1	0.893	CHST12	ACAA1	0.872	DHX58	GPAA1	0.858	PLP2	TSPO	0.845	CYBRD1	NINJ2	0.828
MX1	FLII	0.893	CHST12	FLII	0.872	IFIT3	DNMT1	0.858	PYGL	SLC12A9	0.845	CYBRD1	NRD1	0.828
OAS1	EMR1	0.893	CHST12	LAPTM5	0.872	XAF1	DNMT1	0.858	RAB31	TSPO	0.845	DOK3	IMPA2	0.828
OAS1	PGD	0.893	CHST12	PLP2	0.872	EIF2AK2	PROS1	0.858	RTN3	TBXAS1	0.845	DOK3	SLC12A9	0.828
OAS1	PLP2	0.893	CHST12	PTAFR	0.872	XAF1	GZMB	0.858	SORT1	TSPO	0.845	DOK3	STAT5B	0.828
OAS2	LAPTM5	0.893	CHST12	TBXAS1	0.872	GZMB	RAB31	0.858	IFIT5	CHST12	0.844	DYSF	TALDO1	0.828
SIGLEC1	RTN3	0.893	CUL1	GPAA1	0.872	HESX1	LAPTM5	0.858	PARP12	CHST12	0.844	DYSF	TWF2	0.828
DDX60	SORL1	0.892	CUL1	SORL1	0.872	IFIT3	IFI44L	0.858	CUL1	TNIP1	0.844	PGD	RTN3	0.828
IFIT5	IFI27	0.892	DDX60	PYGL	0.872	RSAD2	IFIT1	0.858	OAS3	DDX60	0.844	PLP2	TALDO1	0.828
IFI44	ACPP	0.892	DHX58	DOK3	0.872	IFIT3	TNIP1	0.858	IFI6	DHX58	0.844	PYGL	RTN3	0.828
IFI44	PTAFR	0.892	DNMT1	LTA4H	0.872	IFIT5	NINJ2	0.858	IFIH1	DHX58	0.844	TALDO1	TBXAS1	0.828
IFI44L	ACPP	0.892	SIGLEC1	EIF2AK2	0.872	IFIT5	TBXAS1	0.858	HESX1	DNMT1	0.844	ADA	RAB31	0.827
ISG15	GPAA1	0.892	EIF2AK2	PYGL	0.872	SIGLEC1	ISG20	0.858	DNMT1	PGD	0.844	IFIT2	DDX60	0.827
ISG15	S100A12	0.892	JUP	HERC5	0.872	ISG20	EMR1	0.858	IFIH1	HERC5	0.844	DHX58	PROS1	0.827
ISG15	TBXAS1	0.892	HERC5	LTA4H	0.872	ISG20	TALDO1	0.858	OAS3	IFIT3	0.844	STAT1	EIF2AK2	0.827
LY6E	IMPA2	0.892	HESX1	IMPA2	0.872	OAS1	JUP	0.858	OASL	IFIT3	0.844	PARP12	IFIH1	0.827
LY6E	SORT1	0.892	SIGLEC1	IFI44	0.872	KCTD14	DYSF	0.858	IFIT5	TWF2	0.844	XAF1	IFIH1	0.827

MX1	TNIP1	0.892	IFI44	TALDO1	0.872	SAMD9	LY6E	0.858	OASL	ISG20	0.844	SAMD9	FLII	0.827
OAS1	PTAFR	0.892	IFI44L	CYBRD1	0.872	STAT1	LY6E	0.858	ISG20	CAT	0.844	ACAA1	TALDO1	0.827
OAS2	CTSB	0.892	IFI44L	PROS1	0.872	OASL	MX1	0.858	ISG20	PYGL	0.844	CETP	HK3	0.827
RSAD2	STAT5B	0.892	IFI44L	PYGL	0.872	OASL	NRD1	0.858	OASL	KCTD14	0.844	CETP	NINJ2	0.827
SIGLEC1	LTA4H	0.892	IFI6	GPAA1	0.872	STAT1	SORL1	0.858	PARP12	KCTD14	0.844	CETP	PGD	0.827
SIGLEC1	NRD1	0.892	IFI6	RTN3	0.872	STAT1	TSPO	0.858	STAT1	OAS2	0.844	CETP	PTAFR	0.827
SIGLEC1	RAB31	0.892	IFI6	TNIP1	0.872	XAF1	TNIP1	0.858	XAF1	OAS3	0.844	CETP	RAB31	0.827
SIGLEC1	TNIP1	0.892	RSAD2	JUP	0.872	ACPP	FLII	0.858	PARP12	CAT	0.844	LAPTM5	PLP2	0.827
IFI44	SORT1	0.891	OAS3	KCTD14	0.872	ACPP	TNIP1	0.858	PARP12	PROS1	0.844	PTAFR	S100A12	0.827
IFI44L	DYSF	0.891	KCTD14	RAB31	0.872	SLC12A9	TNIP1	0.858	XAF1	CAT	0.844	ADA	TALDO1	0.826
IFI44L	HK3	0.891	LY6E	CAT	0.872	SORL1	SORT1	0.858	XAF1	CETP	0.844	SAMD9	EIF2AK2	0.826
IFIT1	LAPTM5	0.891	LY6E	PROS1	0.872	DHX58	ADA	0.857	XAF1	PROS1	0.844	HERC5	IFIT5	0.826
IFIT1	PGD	0.891	MX1	PROS1	0.872	OAS2	CUL1	0.857	ACAA1	SLC12A9	0.844	OAS3	IFIT2	0.826
IFIT1	PLP2	0.891	OAS1	CAT	0.872	CUL1	HK3	0.857	CTSB	SORL1	0.844	STAT1	TKT	0.826
ISG15	RAB31	0.891	SIGLEC1	OAS2	0.872	CUL1	PGD	0.857	CTSB	STAT5B	0.844	CAT	DOK3	0.826
OASL	IMPA2	0.891	OAS2	PROS1	0.872	DDX60	FLII	0.857	EMR1	PROS1	0.844	CAT	S100A12	0.826
DDX60	SLC12A9	0.89	OAS3	RTN3	0.872	DDX60	TNIP1	0.857	EMR1	TSPO	0.844	CETP	CYBRD1	0.826
EIF2AK2	RAB31	0.89	PARP12	HK3	0.872	DHX58	NINJ2	0.857	FLII	RAB31	0.844	CETP	FLII	0.826
SAMD9	IFI27	0.89	RSAD2	CYBRD1	0.872	OAS1	DNMT1	0.857	FLII	SORL1	0.844	CETP	PLP2	0.826
IFI44	SORL1	0.89	RSAD2	TKT	0.872	RSAD2	EIF2AK2	0.857	GPAA1	LAPTM5	0.844	CYBRD1	PTAFR	0.826
IFIH1	SLC12A9	0.89	SAMD9	SORT1	0.872	EIF2AK2	CAT	0.857	MPA2	IPLP2	0.844	DOK3	PYGL	0.826
IFIT1	NRD1	0.89	SIGLEC1	S100A12	0.872	KCTD14	GZMB	0.857	IMPA2	TSPO	0.844	DYSF	PTAFR	0.826
IFIT3	DYSF	0.89	LY6E	ADA	0.871	GZMB	IMPA2	0.857	RAB31	SORT1	0.844	HK3	RAB31	0.826
ISG15	TWF2	0.89	OAS3	CHST12	0.871	IFI44L	HERC5	0.857	RAB31	TNIP1	0.844	HK3	TSPO	0.826
JUP	ACPP	0.89	DHX58	HK3	0.871	IFIT5	IFI44L	0.857	TBXAS1	TNIP1	0.844	NRD1	TNIP1	0.826
LY6E	FLII	0.89	EIF2AK2	LY6E	0.871	PARP12	IFI44L	0.857	HESX1	DDX60	0.843	PGD	TNIP1	0.826
MX1	LTA4H	0.89	EIF2AK2	CETP	0.871	SAMD9	IFI44L	0.857	IFIT3	DDX60	0.843	PGD	TSPO	0.826
MX1	S100A12	0.89	EIF2AK2	TALDO1	0.871	IFIT3	IFI6	0.857	DHX58	TKT	0.843	PTAFR	STAT5B	0.826
MX1	TALDO1	0.89	EIF2AK2	TKT	0.871	OAS3	IFI6	0.857	DNMT1	TBXAS1	0.843	PTAFR	TBXAS1	0.826
OAS2	TWF2	0.89	HERC5	NINJ2	0.871	IFIH1	CTSB	0.857	OASL	HESX1	0.843	PYGL	S100A12	0.826
OAS3	ACPP	0.89	IFI6	HESX1	0.871	IFIH1	GPAA1	0.857	IFIT5	IFI44	0.843	ADA	RTN3	0.825
OAS3	PLP2	0.89	HESX1	RAB31	0.871	IFIH1	NINJ2	0.857	IFIH1	CYBRD1	0.843	CUL1	PROS1	0.825
PARP12	SLC12A9	0.89	IFI44L	CAT	0.871	IFIT2	SORT1	0.857	IFIT2	TKT	0.843	HESX1	DHX58	0.825
RSAD2	RAB31	0.89	IFI6	FLII	0.871	IFIT3	CAT	0.857	OAS3	IFIT5	0.843	DHX58	CYBRD1	0.825
SIGLEC1	PYGL	0.89	ISG15	IFIT1	0.871	IFIT5	NRD1	0.857	IFIT5	LAPTM5	0.843	DNMT1	HK3	0.825
EIF2AK2	DOK3	0.889	SIGLEC1	IFIT1	0.871	XAF1	JUP	0.857	ISG20	SORT1	0.843	PARP12	HESX1	0.825
HERC5	HK3	0.889	IFIT2	PTAFR	0.871	KCTD14	NINJ2	0.857	LAX1	CETP	0.843	STAT1	HESX1	0.825
IFIT3	IFI27	0.889	IFIT5	HK3	0.871	PARP12	DOK3	0.857	OASL	OAS1	0.843	ISG20	CYBRD1	0.825
XAF1	IFI27	0.889	IFIT5	TSPO	0.871	PARP12	LAPTM5	0.857	PARP12	OAS2	0.843	STAT1	TNIP1	0.825
IFIT1	PYGL	0.889	ISG15	PROS1	0.871	SAMD9	ACAA1	0.857	XAF1	CYBRD1	0.843	ACAA1	TKT	0.825
IFIT3	HK3	0.889	ISG20	PLP2	0.871	STAT1	PTAFR	0.857	ACAA1	CAT	0.843	CTSB	DYSF	0.825

ISG15	LAPTM5	0.889	OAS3	JUP	0.871	XAF1	DOK3	0.857	ACPP	TALDO1	0.843	CYBRD1	HK3	0.825
ISG15	NINJ2	0.889	JUP	ACAA1	0.871	XAF1	PGD	0.857	CAT	TNIP1	0.843	EMR1	HK3	0.825
ISG15	PLP2	0.889	JUP	CETP	0.871	ACAA1	SORL1	0.857	CETP	EMR1	0.843	FLII	TBXAS1	0.825
MX1	GPAA1	0.889	LAX1	STAT5B	0.871	ACPP	CETP	0.857	CETP	LTA4H	0.843	LAPTM5	PYGL	0.825
MX1	NINJ2	0.889	OAS1	CETP	0.871	ACPP	RTN3	0.857	CTSB	SORT1	0.843	NINJ2	TBXAS1	0.825
OAS1	CTSB	0.889	OASL	LAPTM5	0.871	CYBRD1	STAT5B	0.857	CYBRD1	LTA4H	0.843	PGD	RAB31	0.825
OAS1	LTA4H	0.889	PARP12	CTSB	0.871	GPAA1	NINJ2	0.857	CYBRD1	PLP2	0.843	PLP2	PROS1	0.825
OAS1	TALDO1	0.889	PARP12	TSPO	0.871	GPAA1	SORT1	0.857	EMR1	NRD1	0.843	PROS1	TSPO	0.825
OAS2	TALDO1	0.889	SAMD9	EMR1	0.871	IMPA2	S100A12	0.857	IMPA2	RAB31	0.843	PTAFR	RAB31	0.825
OAS3	PGD	0.889	ACPP	STAT5B	0.871	NRD1	TBXAS1	0.857	IMPA2	RTN3	0.843	PTAFR	SLC12A9	0.825
RSAD2	IMPA2	0.889	LTA4H	PLP2	0.871	STAT5B	TSPO	0.857	LTA4H	PYGL	0.843	RAB31	TALDO1	0.825
RSAD2	TBXAS1	0.889	CHST12	IFI6	0.87	ADA	LTA4H	0.856	NINJ2	PGD	0.843	TBXAS1	TKT	0.825
SIGLEC1	TKT	0.889	SIGLEC1	CUL1	0.87	CHST12	CTSB	0.856	NINJ2	STAT5B	0.843	CUL1	ADA	0.824
CHST12	SLC12A9	0.888	DDX60	NINJ2	0.87	CHST12	DOK3	0.856	NINJ2	TSPO	0.843	ADA	PYGL	0.824
DDX60	EMR1	0.888	DDX60	NRD1	0.87	CHST12	DYSF	0.856	PROS1	SORT1	0.843	IFIT2	DHX58	0.824
DDX60	HK3	0.888	DHX58	IMPA2	0.87	EIF2AK2	CUL1	0.856	RTN3	S100A12	0.843	EIF2AK2	IFIT5	0.824
DDX60	TSPO	0.888	DHX58	STAT5B	0.87	OAS3	CUL1	0.856	RTN3	SORT1	0.843	IFIT3	IFIT2	0.824
IFI44	EMR1	0.888	RSAD2	DNMT1	0.87	CUL1	TALDO1	0.856	RTN3	TSPO	0.843	STAT1	IFIT3	0.824
IFI44L	STAT5B	0.888	OAS2	GZMB	0.87	RSAD2	DDX60	0.856	SORL1	TKT	0.843	LAX1	PROS1	0.824
LAX1	IFI6	0.888	HERC5	ACAA1	0.87	DDX60	RTN3	0.856	ADA	FLII	0.842	SAMD9	CETP	0.824
IFI6	ACPP	0.888	HERC5	DOK3	0.87	DHX58	LTA4H	0.856	CHST12	PYGL	0.842	STAT1	TWF2	0.824
LAX1	IFIT1	0.888	IFI44	HESX1	0.87	DNMT1	STAT5B	0.856	DDX60	CUL1	0.842	CAT	CYBRD1	0.824
IFIT1	S100A12	0.888	HESX1	DOK3	0.87	GZMB	SORL1	0.856	HERC5	DDX60	0.842	CTSB	PROS1	0.824
IFIT1	TWF2	0.888	HESX1	FLII	0.87	OAS2	HERC5	0.856	PARP12	DDX60	0.842	CYBRD1	LAPTM5	0.824
ISG15	ACAA1	0.888	OAS2	IFI44	0.87	IFIT1	HESX1	0.856	LY6E	DHX58	0.842	DOK3	RAB31	0.824
ISG15	IMPA2	0.888	IFI44	PGD	0.87	OAS1	IFI44	0.856	EIF2AK2	OASL	0.842	DYSF	LAPTM5	0.824
ISG15	LTA4H	0.888	IFI44	PYGL	0.87	IFIT2	IFI44L	0.856	GZMB	NRD1	0.842	FLII	PYGL	0.824
ISG15	NRD1	0.888	ISG20	IFI44L	0.87	LY6E	IFIH1	0.856	HESX1	CYBRD1	0.842	HK3	S100A12	0.824
JUP	HK3	0.888	IFI6	NRD1	0.87	IFIT2	S100A12	0.856	IFI44	STAT1	0.842	HK3	TKT	0.824
KCTD14	SLC12A9	0.888	IFIH1	RAB31	0.87	RSAD2	IFIT3	0.856	IFI6	IFIT5	0.842	LAPTM5	SORT1	0.824
LY6E	GPAA1	0.888	MX1	IFIT1	0.87	SIGLEC1	IFIT3	0.856	IFIH1	PROS1	0.842	LAPTM5	TALDO1	0.824
LY6E	LAPTM5	0.888	LAX1	IFIT3	0.87	XAF1	ISG15	0.856	OAS2	IFIT2	0.842	LAPTM5	TBXAS1	0.824
OAS1	ACPP	0.888	KCTD14	ISG15	0.87	ISG20	LY6E	0.856	OAS1	IFIT3	0.842	PTAFR	SORT1	0.824
OAS1	TWF2	0.888	RSAD2	ISG15	0.87	ISG20	ACPP	0.856	IFIT5	CETP	0.842	PYGL	TNIP1	0.824
OAS2	CETP	0.888	ISG20	GPAA1	0.87	ISG20	NRD1	0.856	PARP12	JUP	0.842	ISG20	CUL1	0.823
OAS3	ACAA1	0.888	JUP	DOK3	0.87	ISG20	TWF2	0.856	KCTD14	CYBRD1	0.842	PARP12	CUL1	0.823
OAS3	DOK3	0.888	KCTD14	CETP	0.87	KCTD14	LY6E	0.856	KCTD14	PROS1	0.842	CUL1	CYBRD1	0.823
OAS3	RAB31	0.888	RSAD2	LY6E	0.87	OAS2	KCTD14	0.856	STAT1	LAX1	0.842	ACAA1	TNIP1	0.823
OASL	TNIP1	0.888	OAS2	MX1	0.87	OAS1	MX1	0.856	LAX1	CTSB	0.842	CAT	TKT	0.823
RSAD2	PTAFR	0.888	OAS1	GPAA1	0.87	PARP12	NRD1	0.856	LAX1	DYSF	0.842	DOK3	TBXAS1	0.823
RSAD2	TSPO	0.888	OAS1	PROS1	0.87	PARP12	TNIP1	0.856	XAF1	OASL	0.842	DYSF	SORT1	0.823

SIGLEC1	NINJ2	0.888	OASL	TKT	0.87	XAF1	CTSB	0.856	STAT1	RSAD2	0.842	FLII	HK3	0.823
EIF2AK2	ADA	0.887	RSAD2	CAT	0.87	XAF1	S100A12	0.856	STAT1	NINJ2	0.842	NRD1	PTAFR	0.823
IFIT1	ADA	0.887	GPAA1	IMPA2	0.87	ACPP	CTSB	0.856	STAT1	RAB31	0.842	PROS1	RTN3	0.823
IFI27	DHX58	0.887	GPAA1	STAT5B	0.87	ACPP	SORT1	0.856	CAT	SORT1	0.842	PYGL	RAB31	0.823
HERC5	EMR1	0.887	LTA4H	SORT1	0.87	CAT	EMR1	0.856	CAT	TSPO	0.842	RAB31	TKT	0.823
HERC5	SORT1	0.887	CHST12	ACPP	0.869	LTA4H	TALDO1	0.856	CETP	TBXAS1	0.842	STAT5B	TNIP1	0.823
IFI44L	SORL1	0.887	ISG15	CUL1	0.869	PLP2	STAT5B	0.856	CTSB	PLP2	0.842	GZMB	ADA	0.822
IFI6	SLC12A9	0.887	CUL1	IMPA2	0.869	KCTD14	ADA	0.855	DOK3	SORL1	0.842	LAX1	CHST12	0.822
IFIT1	FLII	0.887	LY6E	DDX60	0.869	ADA	EMR1	0.855	EMR1	PLP2	0.842	IFIT2	CUL1	0.822
IFIT1	LTA4H	0.887	DDX60	PGD	0.869	CHST12	TKT	0.855	EMR1	TNIP1	0.842	KCTD14	CUL1	0.822
JUP	PLP2	0.887	DHX58	DYSF	0.869	CUL1	FLII	0.855	LTA4H	PROS1	0.842	SAMD9	DHX58	0.822
KCTD14	DOK3	0.887	GZMB	EIF2AK2	0.869	CUL1	RTN3	0.855	PLP2	PYGL	0.842	JUP	DNMT1	0.822
LY6E	ACAA1	0.887	EIF2AK2	GPAA1	0.869	DDX60	TKT	0.855	TSPO	TWF2	0.842	ISG20	IFIT2	0.822
MX1	CTSB	0.887	OASL	GZMB	0.869	GZMB	DHX58	0.855	HESX1	CUL1	0.841	XAF1	IFIT5	0.822
MX1	PYGL	0.887	HERC5	TWF2	0.869	IFIT1	DHX58	0.855	OAS3	DHX58	0.841	SAMD9	TNIP1	0.822
OAS1	ACAA1	0.887	IFI44L	HESX1	0.869	DNMT1	TWF2	0.855	KCTD14	DNMT1	0.841	STAT1	CYBRD1	0.822
OAS1	SORL1	0.887	HESX1	PGD	0.869	GZMB	PLP2	0.855	GZMB	CYBRD1	0.841	CAT	TALDO1	0.822
OASL	TBXAS1	0.887	IFI44	LAPTM5	0.869	GZMB	S100A12	0.855	GZMB	LAPTM5	0.841	CETP	TNIP1	0.822
RSAD2	ACPP	0.887	IFI44	PROS1	0.869	GZMB	TKT	0.855	XAF1	HESX1	0.841	CTSB	FLII	0.822
MX1	ADA	0.886	OAS2	IFI6	0.869	MX1	HERC5	0.855	HESX1	S100A12	0.841	CYBRD1	RAB31	0.822
CUL1	LTA4H	0.886	IFI6	TALDO1	0.869	SIGLEC1	IFIH1	0.855	SAMD9	IFI44	0.841	FLII	PROS1	0.822
EIF2AK2	EMR1	0.886	IFIH1	DOK3	0.869	IFIH1	TNIP1	0.855	SAMD9	IFI6	0.841	NRD1	PROS1	0.822
HERC5	ACPP	0.886	IFIT5	STAT5B	0.869	OAS1	IFIT1	0.855	OASL	IFIH1	0.841	PYGL	TKT	0.822
HERC5	PTAFR	0.886	OAS2	ISG15	0.869	OAS3	IFIT1	0.855	SAMD9	IFIT1	0.841	BXAS1	T TWF2	0.822
HERC5	SLC12A9	0.886	ISG20	TNIP1	0.869	OASL	IFIT1	0.855	LY6E	IFIT2	0.841	ADA	S100A12	0.821
LAX1	IFI44	0.886	SIGLEC1	KCTD14	0.869	IFIT2	PYGL	0.855	IFIT2	STAT5B	0.841	SAMD9	HESX1	0.821
JUP	IFI44L	0.886	LY6E	OAS2	0.869	IFIT3	OAS2	0.855	JUP	IFIT5	0.841	SAMD9	IFIH1	0.821
IFI44L	IMPA2	0.886	OAS3	CETP	0.869	IFIT3	GPAA1	0.855	LAX1	TWF2	0.841	STAT1	CETP	0.821
IFI6	DYSF	0.886	OASL	CETP	0.869	IFIT5	PTAFR	0.855	XAF1	OAS1	0.841	STAT1	FLII	0.821
IFIH1	SORT1	0.886	SAMD9	TSPO	0.869	IFIT5	PYGL	0.855	PARP12	OAS3	0.841	CAT	PYGL	0.821
ISG15	FLII	0.886	FLII	LTA4H	0.869	OAS2	ISG20	0.855	SIGLEC1	OASL	0.841	CTSB	TKT	0.821
JUP	DYSF	0.886	SIGLEC1	CHST12	0.868	OAS1	KCTD14	0.855	STAT1	PLP2	0.841	RTN3	CYBRD1	0.821
JUP	FLII	0.886	CHST12	EMR1	0.868	LAX1	FLII	0.855	STAT1	STAT5B	0.841	DOK3	PROS1	0.821
JUP	SLC12A9	0.886	CIFIT1	UL1	0.868	LAX1	IMPA2	0.855	ACPP	RAB31	0.841	DYSF	PYGL	0.821
LAX1	GPAA1	0.886	DNMT1	DDX60	0.868	LAX1	PGD	0.855	DYSF	TBXAS1	0.841	RTN3	TKT	0.821
LY6E	PLP2	0.886	ISG15	DDX60	0.868	STAT1	EMR1	0.855	EMR1	TALDO1	0.841	ADA	SORT1	0.82
LY6E	TWF2	0.886	EIF2AK2	DNMT1	0.868	STAT1	SORT1	0.855	GPAA1	PTAFR	0.841	PARP12	DHX58	0.82
MX1	LAPTM5	0.886	DNMT1	HERC5	0.868	XAF1	TALDO1	0.855	NINJ2	SORT1	0.841	ISG20	IFIT5	0.82
OAS1	NRD1	0.886	IFI44L	EIF2AK2	0.868	XAF1	TWF2	0.855	PLP2	SORT1	0.841	ACAA1	FLII	0.82
OAS1	S100A12	0.886	EIF2AK2	FLII	0.868	CETP	STAT5B	0.855	SORL1	TALDO1	0.841	ACAA1	LAPTM5	0.82
OAS3	FLII	0.886	EIF2AK2	TWF2	0.868	GPAA1	HK3	0.855	TNIP1	TSPO	0.841	CTSB	DOK3	0.82

OASL	ACPP	0.886	LY6E	GZMB	0.868	GPAA1	PYGL	0.855	ADA	ACAA1	0.84	CYBRD1	TALDO1	0.82
OASL	DOK3	0.886	HERC5	LAPTM5	0.868	IMPA2	SLC12A9	0.855	ADA	STAT5B	0.84	DYSF	HK3	0.82
RSAD2	LTA4H	0.886	HERC5	PYGL	0.868	LAPTM5	SORL1	0.855	OAS1	DHX58	0.84	DYSF	TKT	0.82
DHX58	EMR1	0.885	HESX1	DYSF	0.868	LTA4H	RAB31	0.855	DNMT1	ACAA1	0.84	DYSF	TNIP1	0.82
DHX58	SLC12A9	0.885	IFIT1	IFI44L	0.868	LTA4H	S100A12	0.855	DNMT1	TNIP1	0.84	HK3	LAPTM5	0.82
DHX58	SORT1	0.885	MX1	IFI44L	0.868	RAB31	SORL1	0.855	SAMD9	GZMB	0.84	NINJ2	PLP2	0.82
IFI44	TBXAS1	0.885	JUP	IFI6	0.868	SORT1	STAT5B	0.855	XAF1	HERC5	0.84	NINJ2	PROS1	0.82
IFI44	TSPO	0.885	IFIH1	LTA4H	0.868	PARP12	ADA	0.854	ISG20	HESX1	0.84	PGD	PTAFR	0.82
IFIH1	PTAFR	0.885	IFIT2	DYSF	0.868	CHST12	RAB31	0.854	IFIT2	IFI44	0.84	PGD	PYGL	0.82
IFIT3	SLC12A9	0.885	IFIT2	SLC12A9	0.868	CUL1	DYSF	0.854	IFIT2	IFIT1	0.84	PROS1	S100A12	0.82
MX1	LAX1	0.885	IFIT3	S100A12	0.868	IFI44L	DDX60	0.854	RSAD2	IFIT2	0.84	PROS1	TNIP1	0.82
LY6E	CTSB	0.885	IFIT3	STAT5B	0.868	DHX58	TNIP1	0.854	SIGLEC1	IFIT2	0.84	PYGL	TALDO1	0.82
LY6E	DOK3	0.885	IFIT3	TSPO	0.868	DHX58	TWF2	0.854	KCTD14	IFIT5	0.84	ADA	LAPTM5	0.819
LY6E	S100A12	0.885	IFIT5	EMR1	0.868	HESX1	EIF2AK2	0.854	LAX1	DOK3	0.84	CUL1	CHST12	0.819
LY6E	STAT5B	0.885	IFIT5	IMPA2	0.868	EIF2AK2	JUP	0.854	PARP12	OAS1	0.84	SAMD9	CUL1	0.819
MX1	TKT	0.885	OAS3	ISG15	0.868	JUP	GZMB	0.854	ACPP	TBXAS1	0.84	STAT1	DDX60	0.819
MX1	TWF2	0.885	JUP	NRD1	0.868	GZMB	GPAA1	0.854	ACPP	TKT	0.84	CETP	PYGL	0.819
OAS1	FLII	0.885	JUP	PYGL	0.868	GZMB	TALDO1	0.854	CAT	PLP2	0.84	PYGL	CYBRD1	0.819
OAS2	PYGL	0.885	KCTD14	TBXAS1	0.868	GZMB	TBXAS1	0.854	CAT	STAT5B	0.84	DOK3	EMR1	0.819
OAS2	S100A12	0.885	MX1	LY6E	0.868	HESX1	HERC5	0.854	CAT	TBXAS1	0.84	HK3	SORT1	0.819
OASL	RAB31	0.885	SIGLEC1	LY6E	0.868	IFIT1	HERC5	0.854	CTSB	EMR1	0.84	RTN3	TALDO1	0.819
PARP12	SORT1	0.885	OASL	LTA4H	0.868	OAS1	HESX1	0.854	CYBRD1	TNIP1	0.84	DNMT1	GZMB	0.818
RSAD2	NINJ2	0.885	PARP12	IMPA2	0.868	HESX1	PYGL	0.854	FLII	SLC12A9	0.84	IFIT2	HESX1	0.818
RSAD2	S100A12	0.885	PARP12	RAB31	0.868	XAF1	IFI44L	0.854	HK3	NINJ2	0.84	XAF1	IFIT2	0.818
GPAA1	SORL1	0.885	SIGLEC1	RSAD2	0.868	IFIH1	CAT	0.854	HK3	SORL1	0.84	XAF1	SAMD9	0.818
IFI44	ADA	0.884	SAMD9	RAB31	0.868	IFIH1	CETP	0.854	IMPA2	PGD	0.84	CTSB	CAT	0.818
CUL1	SLC12A9	0.884	SAMD9	S100A12	0.868	IFIT3	CETP	0.854	LAPTM5	STAT5B	0.84	CETP	TKT	0.818
DDX60	ACPP	0.884	ACAA1	LTA4H	0.868	IFIT5	ACAA1	0.854	PGD	SORL1	0.84	CTSB	PTAFR	0.818
EIF2AK2	ACAA1	0.884	PLP2	SORL1	0.868	STAT1	ISG15	0.854	PLP2	TBXAS1	0.84	TNIP1	CTSB	0.818
EIF2AK2	LAPTM5	0.884	RAB31	SLC12A9	0.868	ISG20	FLII	0.854	PROS1	TBXAS1	0.84	DOK3	NRD1	0.818
EIF2AK2	S100A12	0.884	CHST12	TSPO	0.867	ISG20	LAPTM5	0.854	PYGL	STAT5B	0.84	DOK3	SORT1	0.818
IFI44	GZMB	0.884	IFI44	CUL1	0.867	ISG20	TBXAS1	0.854	RTN3	TNIP1	0.84	DOK3	TSPO	0.818
IFI44L	ACAA1	0.884	DDX60	PLP2	0.867	SAMD9	JUP	0.854	S100A12	TALDO1	0.84	HK3	TALDO1	0.818
IFI44L	TBXAS1	0.884	SIGLEC1	HERC5	0.867	JUP	CAT	0.854	SLC12A9	STAT5B	0.84	LAPTM5	PGD	0.818
IFI6	PLP2	0.884	HERC5	CTSB	0.867	KCTD14	CTSB	0.854	ADA	PTAFR	0.839	PGD	TALDO1	0.818
IFI6	PTAFR	0.884	HESX1	GPAA1	0.867	OAS2	OAS1	0.854	JUP	CUL1	0.839	PROS1	PYGL	0.818
IFI6	RAB31	0.884	HESX1	RTN3	0.867	OAS3	OAS2	0.854	XAF1	CUL1	0.839	PTAFR	TWF2	0.818
IFI6	S100A12	0.884	HESX1	STAT5B	0.867	PARP12	PYGL	0.854	HERC5	DHX58	0.839	TALDO1	TNIP1	0.818
IFIT1	CTSB	0.884	IFI44	FLII	0.867	PARP12	TWF2	0.854	PARP12	EIF2AK2	0.839	ADA	DOK3	0.817
IFIT3	PTAFR	0.884	IFI44	TKT	0.867	SAMD9	NRD1	0.854	OAS1	IFIH1	0.839	DNMT1	CUL1	0.817
ISG15	CTSB	0.884	RSAD2	IFI44L	0.867	XAF1	LAPTM5	0.854	JUP	ISG20	0.839	IFIT5	IFIH1	0.817
ISG15	PYGL	0.884	IFI6	CETP	0.867	XAF1	RAB31	0.854	ISG20	PROS1	0.839	PARP12	IFIT5	0.817

JUP	RAB31	0.884	IFI6	TKT	0.867	CTSB	TSPO	0.854	LAX1	TALDO1	0.839	SAMD9	PARP12	0.817
JUP	TBXAS1	0.884	IFIH1	S100A12	0.867	DYSF	LTA4H	0.854	STAT1	PGD	0.839	STAT1	LAPTM5	0.817
OAS2	LAX1	0.884	IFIH1	TBXAS1	0.867	EMR1	RTN3	0.854	ACAA1	IMPA2	0.839	ACAA1	HK3	0.817
LY6E	SORL1	0.884	ISG20	IFIT1	0.867	EMR1	STAT5B	0.854	ACAA1	TBXAS1	0.839	ACAA1	TWF2	0.817
OAS1	NINJ2	0.884	IFIT3	PLP2	0.867	PLP2	SLC12A9	0.854	ACPP	DYSF	0.839	CAT	PROS1	0.817
OAS1	TKT	0.884	IFIT3	RAB31	0.867	S100A12	STAT5B	0.854	ACPP	NINJ2	0.839	FLII	PGD	0.817
OAS2	RTN3	0.884	ISG20	IMPA2	0.867	IFIT1	DDX60	0.853	ACPP	TWF2	0.839	HK3	PYGL	0.817
OASL	S100A12	0.884	ISG20	TSPO	0.867	MX1	DDX60	0.853	CAT	FLII	0.839	LAPTM5	TNIP1	0.817
RSAD2	DOK3	0.884	JUP	S100A12	0.867	DDX60	CETP	0.853	CAT	PGD	0.839	NINJ2	TKT	0.817
RSAD2	LAPTM5	0.884	KCTD14	IMPA2	0.867	MX1	DHX58	0.853	CYBRD1	DYSF	0.839	TKT	TNIP1	0.817
RSAD2	PLP2	0.884	KCTD14	TALDO1	0.867	PARP12	DNMT1	0.853	CYBRD1	TSPO	0.839	CHST12	ADA	0.816
RSAD2	TWF2	0.884	PARP12	PLP2	0.867	DNMT1	SLC12A9	0.853	DYSF	NINJ2	0.839	IFIT5	CUL1	0.816
SIGLEC1	CETP	0.884	XAF1	ACPP	0.867	DNMT1	TKT	0.853	NRD1	RAB31	0.839	PARP12	IFIT2	0.816
GPAA1	LTA4H	0.884	GPAA1	TALDO1	0.867	GZMB	CTSB	0.853	NRD1	SORL1	0.839	CAT	NINJ2	0.816
ISG15	DNMT1	0.883	OAS1	ADA	0.866	GZMB	SLC12A9	0.853	SORT1	NRD1	0.839	DYSF	FLII	0.816
ISG15	EIF2AK2	0.883	EIF2AK2	IFI44	0.866	IFI44	HERC5	0.853	NRD1	TKT	0.839	PGD	TWF2	0.816
EIF2AK2	PTAFR	0.883	OAS1	GZMB	0.866	ISG20	HERC5	0.853	PLP2	S100A12	0.839	PROS1	TKT	0.816
IFI44L	NRD1	0.883	SIGLEC1	GZMB	0.866	HESX1	TNIP1	0.853	S100A12	TKT	0.839	PTAFR	TNIP1	0.816
IFI44L	PLP2	0.883	HERC5	PGD	0.866	PARP12	IFI44	0.853	ADA	CETP	0.838	TKT	TWF2	0.816
IFI44L	SORT1	0.883	LAX1	HESX1	0.866	OAS1	IFI6	0.853	ADA	TKT	0.838	STAT1	DHX58	0.815
IFI44L	TSPO	0.883	MX1	HESX1	0.866	OAS2	IFIH1	0.853	IFIT2	CHST12	0.838	DNMT1	NINJ2	0.815
IFI6	TBXAS1	0.883	HESX1	CTSB	0.866	IFIT3	CYBRD1	0.853	CHST12	CYBRD1	0.838	KCTD14	IFIT2	0.815
IFIT1	TNIP1	0.883	HESX1	HK3	0.866	IFIT5	DOK3	0.853	CUL1	CETP	0.838	ACAA1	NINJ2	0.815
JUP	PTAFR	0.883	HESX1	PTAFR	0.866	IFIT5	RTN3	0.853	IFIH1	DDX60	0.838	ACAA1	PTAFR	0.815
JUP	TALDO1	0.883	IFI44	ISG20	0.866	ISG20	DYSF	0.853	DNMT1	ACPP	0.838	CYBRD1	PROS1	0.815
JUP	TNIP1	0.883	IFI44	CYBRD1	0.866	KCTD14	PYGL	0.853	DNMT1	PTAFR	0.838	DYSF	DOK3	0.815
RSAD2	LAX1	0.883	IFI6	IFI44L	0.866	RSAD2	OAS1	0.853	HESX1	PROS1	0.838	HK3	PTAFR	0.815
LY6E	ACPP	0.883	KCTD14	IFI6	0.866	PARP12	FLII	0.853	IFI6	IFIT2	0.838	NINJ2	PTAFR	0.815
LY6E	RAB31	0.883	MX1	IFI6	0.866	PARP12	S100A12	0.853	IFIH1	OAS3	0.838	NINJ2	TNIP1	0.815
MX1	RTN3	0.883	IFI6 RSAD2		0.866	SAMD9	PGD	0.853	JUP	IFIT2	0.838	PROS1	RAB31	0.815
OAS1	PYGL	0.883	IFIH1	IMPA2	0.866	SIGLEC1	CYBRD1	0.853	IFIT2	ACAA1	0.838	CETP	DOK3	0.814
OAS2	TKT	0.883	IFIH1	STAT5B	0.866	STAT1	IMPA2	0.853	IFIT2	CAT	0.838	CTSB	LAPTM5	0.814
OAS3	CTSB	0.883	LY6E	IFIT1	0.866	XAF1	LTA4H	0.853	IFIT2	CYBRD1	0.838	TKT	CYBRD1	0.814
OASL	PLP2	0.883	IFIT3	DOK3	0.866	CYBRD1	SORL1	0.853	LAX1	S100A12	0.838	FLII	TNIP1	0.814
RSAD2	NRD1	0.883	IFIT3	TALDO1	0.866	DYSF	GPAA1	0.853	SAMD9	TALDO1	0.838	LAPTM5	NINJ2	0.814
LAX1	EIF2AK2	0.882	ISG20	ISG15	0.866	EMR1	SLC12A9	0.853	SAMD9	TWF2	0.838	PLP2	TWF2	0.814
IFI44L	GZMB	0.882	SIGLEC1	JUP	0.866	IFIH1	ADA	0.852	ACAA1	CETP	0.838	PROS1	TWF2	0.814
ISG15	GZMB	0.882	KCTD14	NRD1	0.866	ADA	TWF2	0.852	ACAA1	SORT1	0.838	CETP	LAPTM5	0.813
HESX1	ACAA1	0.882	PARP12	LAX1	0.866	CUL1	SORT1	0.852	CTSB	RTN3	0.838	CETP	TALDO1	0.813
JUP	IFI44	0.882	LAX1	SLC12A9	0.866	CUL1	STAT5B	0.852	SLC12A9	CTSB	0.838	DOK3	NINJ2	0.813
IFI44	ACAA1	0.882	MX1	CYBRD1	0.866	IFI44L	DHX58	0.852	GPAA1	DOK3	0.838	DYSF	PGD	0.813

LAX1	IFI44L	0.882	SAMD9	ACPP	0.866	DHX58	PYGL	0.852	FLII	NRD1	0.838	TNIP1	TWF2	0.813
IFI44L	CTSB	0.882	SAMD9	PTAFR	0.866	DNMT1	IMPA2	0.852	GPAA1	TWF2	0.838	DOK3	PLP2	0.812
IFI44L	NINJ2	0.882	GPAA1	TSPO	0.866	EIF2AK2	CYBRD1	0.852	IMPA2	NINJ2	0.838	FLII	TALDO1	0.812
IFI6	ACAA1	0.882	SORL1	S100A12	0.866	HESX1	GZMB	0.852	IMPA2	PYGL	0.838	LAPTM5	PROS1	0.812
IFI6	IMPA2	0.882	CHST12	LTA4H	0.865	GZMB	TWF2	0.852	NRD1	STAT5B	0.838	NINJ2	TALDO1	0.812
IFIH1	HK3	0.882	CHST12	PGD	0.865	RSAD2	HERC5	0.852	PYGL	SORL1	0.838	PGD	TKT	0.812
IFIT1	TALDO1	0.882	CHST12	SORL1	0.865	OASL	IFI6	0.852	RAB31	TWF2	0.838	TWF2	TALDO1	0.812
IFIT1	TKT	0.882	CUL1	MX1	0.865	LAX1	IFIT2	0.852	CUL1	DOK3	0.837	SAMD9	IFIT2	0.811
JUP	ISG15	0.882	DDX60	GZMB	0.865	IFIT2	CTSB	0.852	IFIT3	DHX58	0.837	STAT1	ISG20	0.811
SIGLEC1	ISG15	0.882	DHX58	ACAA1	0.865	LY6E	IFIT5	0.852	EIF2AK2	XAF1	0.837	XAF1	STAT1	0.811
ISG15	TKT	0.882	EIF2AK2	IFIT1	0.865	IFIT5	CAT	0.852	IFIT5	GZMB	0.837	CETP	TWF2	0.811
JUP	GPAA1	0.882	EIF2AK2	OAS2	0.865	ISG20	HK3	0.852	GZMB	DOK3	0.837	HK3	PGD	0.811
JUP	LTA4H	0.882	GZMB	LTA4H	0.865	OASL	OAS2	0.852	PARP12	HERC5	0.837	PTAFR	TALDO1	0.811
LY6E	NINJ2	0.882	GZMB	PGD	0.865	PARP12	RTN3	0.852	IFIT2	NRD1	0.837	PARP12	STAT1	0.81
LY6E	TALDO1	0.882	GZMB	TSPO	0.865	PARP12	TKT	0.852	IFIT3	ISG20	0.837	ACAA1	DOK3	0.81
MX1	CETP	0.882	HERC5	PROS1	0.865	SAMD9	NINJ2	0.852	LAX1	PYGL	0.837	FLII	PTAFR	0.81
OAS1	DOK3	0.882	HERC5	TALDO1	0.865	SAMD9	PLP2	0.852	OASL	PARP12	0.837	TKT	LAPTM5	0.81
OAS1	STAT5B	0.882	IFI44	CETP	0.865	SIGLEC1	STAT1	0.852	STAT1	OASL	0.837	DNMT1	DOK3	0.809
OAS1	TNIP1	0.882	IFI44	RTN3	0.865	STAT1	DYSF	0.852	STAT1	TALDO1	0.837	PTAFR	LAPTM5	0.809
OAS3	LAPTM5	0.882	IFI44L	OASL	0.865	XAF1	FLII	0.852	ACAA1	ACPP	0.837	PTAFR	TKT	0.809
OAS3	TALDO1	0.882	IFI6	PYGL	0.865	XAF1	TKT	0.852	ACAA1	CTSB	0.837	STAT1	IFIT5	0.808
OAS3	TNIP1	0.882	IFIH1	NRD1	0.865	ACPP	IMPA2	0.852	ACAA1	PYGL	0.837	TWF2	LAPTM5	0.808
OASL	NINJ2	0.882	IFIH1	PLP2	0.865	CAT	SORL1	0.852	ACPP	S100A12	0.837	PROS1	TALDO1	0.808
RSAD2	ACAA1	0.882	IFIH1	PYGL	0.865	CETP	SORT1	0.852	DYSF	NRD1	0.837	DNMT1	SORT1	0.807
RSAD2	CTSB	0.882	OAS2	IFIT1	0.865	CTSB	LTA4H	0.852	TBXAS1	EMR1	0.837	ADA	LAX1	0.806
RSAD2	TNIP1	0.882	IFIT2	ACPP	0.865	CTSB	RAB31	0.852	EMR1	TKT	0.837	DOK3	HK3	0.806
SAMD9	HK3	0.882	IFIT3	PGD	0.865	DOK3	LTA4H	0.852	HK3	RTN3	0.837	SAMD9	IFIT5	0.805
SAMD9	SLC12A9	0.882	ISG20	LTA4H	0.865	EMR1	IMPA2	0.852	IMPA2	LAPTM5	0.837	DOK3	PTAFR	0.805
LTA4H	SLC12A9	0.882	KCTD14	PTAFR	0.865	FLII	S100A12	0.852	PYGL	SORT1	0.837	FLII	TKT	0.805
MX1	DNMT1	0.881	OAS2	CYBRD1	0.865	GPAA1	TNIP1	0.852	TBXAS1	SORT1	0.837	DNMT1	CHST12	0.804
EIF2AK2	ACPP	0.881	SIGLEC1	OAS3	0.865	IMPA2	SORL1	0.852	TBXAS1	TSPO	0.837	IFIT2	IFIH1	0.804
EIF2AK2	TNIP1	0.881	OASL	GPAA1	0.865	NINJ2	SORL1	0.852	ADA	CTSB	0.836	NINJ2	TWF2	0.804
HERC5	DYSF	0.881	PARP12	LTA4H	0.865	STAT5B	TWF2	0.852	CUL1	LAPTM5	0.836	STAT1	IFIH1	0.803
IFI44L	RAB31	0.881	SAMD9	IMPA2	0.865	CHST12	IFIH1	0.851	XAF1	DDX60	0.836	IFIT5	IFIT2	0.803
IFI44L	S100A12	0.881	SAMD9	SORL1	0.865	CHST12	S100A12	0.851	DNMT1	DYSF	0.836	CETP	PROS1	0.802
IFI6	NINJ2	0.881	XAF1	TSPO	0.865	IFI44	DHX58	0.851	DNMT1	PLP2	0.836	DOK3	TKT	0.802
IFI6	PGD	0.881	CETP	SLC12A9	0.865	DHX58	CTSB	0.851	DNMT1	RAB31	0.836	FLII	TWF2	0.802
IFI6	TWF2	0.881	GPAA1	NRD1	0.865	DHX58	NRD1	0.851	GZMB	STAT5B	0.836	STAT1	IFIT2	0.801
IFIT1	RTN3	0.881	GPAA1	TBXAS1	0.865	DHX58	RTN3	0.851	IFIT2	CETP	0.836	SAMD9	STAT1	0.8
IFIT3	EMR1	0.881	LAPTM5	LTA4H	0.865	SAMD9	DNMT1	0.851	IFIT2	FLII	0.836	DOK3	TWF2	0.8
IFIT3	SORL1	0.881	CHST12	HERC5	0.864	EIF2AK2	ISG20	0.851	IFIT5	FLII	0.836			

JUP	RTN3	0.881	CHST12	OAS1	0.864	IFIT2	GZMB	0.851	IFIT5	GPAA1	0.836
JUP	TWF2	0.881	OAS2	CHST12	0.864	GZMB	HK3	0.851	XAF1	ISG20	0.836
KCTD14	SORT1	0.881	CHST12	SORT1	0.864	GZMB	NINJ2	0.851	LAX1	RAB31	0.836
LAX1	SORL1	0.881	OAS2	DDX60	0.864	GZMB	PROS1	0.851	SAMD9	GPAA1	0.836
OAS3	LTA4H	0.881	DDX60	S100A12	0.864	HESX1	CETP	0.851	STAT1	CTSB	0.836
OAS3	PYGL	0.881	DHX58	PLP2	0.864	IFIT3	IFI44	0.851	ACAA1	CYBRD1	0.836
OASL	ACAA1	0.881	OAS2	DNMT1	0.864	IFIH1	IFI6	0.851	ACAA1	TSPO	0.836
PARP12	EMR1	0.881	DNMT1	FLII	0.864	IFIT2	LTA4H	0.851	CYBRD1	ACPP	0.836
XAF1	SLC12A9	0.881	EIF2AK2	MX1	0.864	IFIT2	PGD	0.851	ACPP	HK3	0.836

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While the preferred embodiments of the invention have been illustrated and 25 described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

Claims

What is claimed is:

5 1. A method for diagnosing an infection in a patient, the method comprising:

a) measuring levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral
10 infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers
15 comprise at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB; and

b) analyzing the levels of expression of each biomarker in conjunction with
20 respective reference value ranges for the biomarkers to determine a viral or bacterial infection.

2. The method of claim 1, wherein the at least two biomarkers include SIGLEC1 and SLC12A9.

25

3. The method of any prior claim, wherein the levels of expression of the at least two biomarkers provide an area under a receiver operating characteristic curve of at least 0.80.

30 4. The method of any prior claim, wherein the first set of biomarkers comprise at least one of HK3, TNIP1, GPAA1, and CTSB; and wherein the second set of biomarkers comprise at least one of IFI27, JUP, and LAX1

5. The method of any prior claim, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

6. The method of any prior claim, wherein the levels of the biomarkers are compared to time-matched reference values for infected or non-infected subjects.

7. The method of any prior claim, further comprising calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

8. The method of any prior claim, further comprising normalizing data using COCONUT normalization; COCONUT normalization comprising the steps of:

a) separating data from multiple cohorts into healthy and diseased components;

b) co-normalizing the healthy components using ComBat co-normalization without covariates;

c) obtaining ComBat estimated parameters for each dataset for the healthy component; and

d) applying the ComBat estimated parameters onto the diseased component.

9. The method of any prior claim, wherein the patient is a human being.

10. The method of any prior claim, wherein measuring the level of the biomarkers comprises performing one or more methods including microarray analysis via fluorescence, chemiluminesence, or electric signal detection, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), digital droplet PCR (ddPCR), solid-state nanopore detection, RNA switch activation, a Northern blot, or a serial analysis of gene expression (SAGE).

11. A method of diagnosing and treating a patient having inflammation, the method comprising:

a) measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370,

TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in a biological sample of the patient; and

b) first analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, wherein increased levels of expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection; and

c) further analyzing the levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB to determine a bacterial or viral infection.

12. The method of claim 11, further comprising calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition.

13. The method of any of claims 11-12, further comprising calculating a bacterial/viral metascore for the patient if the patient is diagnosed as having an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

14. The method of any of claims 11-13, wherein the levels of the biomarkers are compared to time-matched reference values for infected or non-infected subjects.

15. The method of any of claims 11-14, wherein the non-infectious inflammatory condition is selected from the group consisting of systemic inflammatory response syndrome (SIRS), an autoimmune disorder, a traumatic injury, and surgery.

16. The method of any of claims 11-15, wherein the patient is a human being.

17. The method of any of claims 11-16, wherein measuring the levels of the biomarkers comprises performing one or more methods including microarray analysis via fluorescence, chemiluminesence, or electric signal detection, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), digital droplet PCR (ddPCR), solid-state nanopore detection, RNA switch activation, a Northern blot, or a serial analysis of gene expression (SAGE).

18. A kit comprising agents for measuring levels of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12,

LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB.

19. The kit of claim 18, further comprising agents for measuring the levels of CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers.

20. The kit of any of claims 18-19, further comprising a microarray.

21. The kit of claim 20, wherein the microarray comprises an oligonucleotide that hybridizes to an IFI27 polynucleotide, an oligonucleotide that hybridizes to a JUP polynucleotide, an oligonucleotide that hybridizes to a LAX1 polynucleotide, an oligonucleotide that hybridizes to a HK3 polynucleotide, an oligonucleotide that hybridizes to a TNIP1 polynucleotide, an oligonucleotide that hybridizes to a GPAA1 polynucleotide, and an oligonucleotide that hybridizes to a CTSB polynucleotide

22. The kit of claim 20, wherein the microarray further comprising an oligonucleotide that hybridizes to a CEACAM1 polynucleotide, an oligonucleotide that hybridizes to a ZDHHC19 polynucleotide, an oligonucleotide that hybridizes to a C9orf95 polynucleotide, an oligonucleotide that hybridizes to a GNA15 polynucleotide, an oligonucleotide that hybridizes to a BATF polynucleotide, an oligonucleotide that hybridizes to a C3AR1 polynucleotide, an oligonucleotide that hybridizes to a KIAA1370 polynucleotide, an oligonucleotide that hybridizes to a TGFBI polynucleotide, an oligonucleotide that hybridizes to a MTCH1 polynucleotide, an oligonucleotide that hybridizes to a RPGRIP1 polynucleotide, and an oligonucleotide that hybridizes to a HLA-DPB1 polynucleotide.

23. The kit of any of claims 18-22, further comprising information, in electronic or paper form, comprising instructions to correlate the detected levels of each biomarker with sepsis.

24. A computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps comprising:

a) receiving inputted patient data comprising values for levels of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level
5 of expression indicates a viral infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the
10 second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB biomarkers in the biological sample from the patient;
15 b) analyzing the level of each of the biomarkers and comparing with respective reference value ranges for the biomarkers;
c) calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient
20 indicates that the patient has a bacterial infection; and
d) displaying information regarding the diagnosis of the patient.

25. The method of claim 24, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

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26. A diagnostic system for performing the method of claim 24, comprising:
a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein;
b) a computer processor for processing data, wherein the computer processor is
30 coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and
c) a display component for displaying information regarding the diagnosis of the patient.

27. The diagnostic system of claim 26, wherein the storage component comprises instructions for calculating the bacterial/viral metascore.

5 28. A computer implemented method for diagnosing a patient having inflammation, the computer performing steps comprising:

a) receiving inputted patient data comprising values for the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1
10 biomarkers in a biological sample from the patient;

b) analyzing the levels of each of the biomarkers and comparing with respective reference value ranges for the biomarkers;

c) calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates
15 that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition;

d) calculating a bacterial/viral metascore for the patient if the sepsis metascore indicates that the patient has an infection, wherein a positive bacterial/viral metascore
20 for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and

e) displaying information regarding the diagnosis of the patient.

25 29. The method of claim 28, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

30. A diagnostic system for performing the method of claim 28, comprising:

a) a storage component for storing data, wherein the storage component has
30 instructions for determining the diagnosis of the patient stored therein;

b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and

c) a display component for displaying information regarding the diagnosis of the patient.

31. The diagnostic system of claim 30, wherein the storage component comprises instructions for calculating the sepsis metascore and the bacterial/viral metascore.

32. A method for diagnosing and treating an infection in a patient, the method comprising:

a) obtaining a biological sample from the patient;

b) measuring the levels of expression of any set of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB; and

c) analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for a noninfected control subject, wherein differential expression of the viral response genes compared to the reference value ranges for a noninfected control subject indicate that the patient has a viral infection, and differential expression of the bacterial response genes compared to the reference value ranges for a noninfected control subject indicate that the patient has a bacterial infection.

33. The method of claim 32, wherein the set of viral and bacterial response genes are selected from the group consisting of:

a) a set of viral response genes comprising OAS2 and CUL1 and a set of bacterial response genes comprising SLC12A9, ACPP, STAT5B;

b) a set of viral response genes comprising ISG15 and CHST12 and a set of bacterial response genes comprising EMR1 and FLII;

c) a set of viral response genes comprising IFIT1, SIGLEC1, and ADA and a set of bacterial response genes comprising PTAFR, NRD1, PLP2;

5 d) a set of viral response genes comprising MX1 and a set of bacterial response genes comprising DYSF, TWF2;

e) a set of viral response genes comprising RSAD2 and a set of bacterial response genes comprising SORT1 and TSPO;

f) a set of viral response genes comprising IFI44L, GZMB, and KCTD14 and a

10 set of bacterial response genes comprising TBXAS1, ACAA1, and S100A12;

g) a set of viral response genes comprising LY6E and a set of bacterial response genes comprising PGD and LAPTM5;

h) a set of viral response genes comprising IFI44, HESX1, and OASL and a set of bacterial response genes comprising NINJ2, DOK3, SORL1, and RAB31;

15 i) a set of viral response genes comprising OAS1 and a set of bacterial response genes comprising IMPA2 and LTA4H.

34. The method of any of claims 32-33, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

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35. The method of of claims 32-34, wherein the levels of the biomarkers are compared to time-matched reference values for infected or non-infected subjects.

36. The method of of claims 32-35, further comprising calculating a bacterial/viral

25 metascore for the patient t based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

30 37. The method of of claims 32-36, further comprising measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in the biological sample; and analyzing the levels of expression of each biomarker in conjunction with respective reference value

ranges for the biomarkers, wherein increased levels of expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection.

38. A kit comprising agents for measuring the levels of expression of a set of viral response genes and a set of bacterial response genes selected from the group consisting of:

a) a set of viral response genes comprising OAS2 and CUL1 and a set of bacterial response genes comprising SLC12A9, ACPP, STAT5B;

b) a set of viral response genes comprising ISG15 and CHST12 and a set of bacterial response genes comprising EMR1 and FLII;

c) a set of viral response genes comprising IFIT1, SIGLEC1, and ADA and a set of bacterial response genes comprising PTAFR, NRD1, PLP2;

d) a set of viral response genes comprising MX1 and a set of bacterial response genes comprising DYSF, TWF2;

e) a set of viral response genes comprising RSAD2 and a set of bacterial response genes comprising SORT1 and TSPO;

f) a set of viral response genes comprising IFI44L, GZMB, and KCTD14 and a set of bacterial response genes comprising TBXAS1, ACAA1, and S100A12;

g) a set of viral response genes comprising LY6E and a set of bacterial response genes comprising PGD and LAPTM5;

h) a set of viral response genes comprising IFI44, HESX1, and OASL and a set of bacterial response genes comprising NINJ2, DOK3, SORL1, and RAB31; and

i) a set of viral response genes comprising OAS1 and a set of bacterial response genes comprising IMPA2 and LTA4H.

39. The kit of claim 38, further comprising a microarray.

40. A computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps comprising:

a) receiving inputted patient data comprising values for the levels of expression of at least two biomarkers in a biological sample of a patient; the at least two
5 biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection, wherein the set of viral response genes comprises one or more genes selected from the group consisting of OAS2, CUL1, ISG15, CHST12, IFIT1, SIGLEC1, ADA, MX1, RSAD2, IFI44L,
10 GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, HERC5, IFIH1, SAMD9, IFI6, IFIT3, IFIT5, XAF1, ISG20, PARP12, IFIT2, DHX58, STAT1, and the set of bacterial response genes comprises one or more genes selected from the group consisting of SLC12A9, ACPP, STAT5B, EMR1, FLII, PTAFR, NRD1, PLP2, DYSF, TWF2, SORT1, TSPO, TBXAS1, ACAA1,
15 S100A12, PGD, LAPTM5, NINJ2, DOK3, SORLI, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT, CYBRD1;

b) analyzing the levels of expression of the set of viral response genes and the set of bacterial response genes and comparing with respective reference value ranges for a noninfected control subject;

20 c) calculating a bacterial/viral metascore for the patient based on the levels of expression of the set of viral response genes and the set of bacterial response genes; and

d) displaying information regarding the diagnosis of the patient.

25 41. A diagnostic system for performing the method of claim 40, comprising:

a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein;

b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in
30 the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and

c) a display component for displaying information regarding the diagnosis of the patient.

AMENDED CLAIMS
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What is claimed is:

1. A method for diagnosing an infection in a patient, the method comprising:

a) measuring levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, DDX60, HESX1, OASL, LAX1, IFIT5, KCTD14, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB; and

b) analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers to determine a viral or bacterial infection.

2. The method of claim 1, wherein the at least two biomarkers include SIGLEC1 and SLC12A9.

3. The method of any prior claim, wherein the levels of expression of the at least two biomarkers provide an area under a receiver operating characteristic curve of at least 0.80.

4. The method of claim 1, wherein the first set of biomarkers comprise at least one of HK3, TNIP1, GPAA1, and CTSB; and wherein the second set of biomarkers comprise at least one of IFI27, JUP, and LAX1

5. The method of claim 1, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

6. The method of claim 1, wherein the levels of the biomarkers are compared to time-matched reference values for infected or non-infected subjects.

7. The method of claim 1, further comprising calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

8. The method of claim 1, further comprising normalizing data using COCONUT normalization; COCONUT normalization comprising the steps of:

a) separating data from multiple cohorts into healthy and diseased components;

b) co-normalizing the healthy components using ComBat co-normalization without covariates;

c) obtaining ComBat estimated parameters for each dataset for the healthy component; and

d) applying the ComBat estimated parameters onto the diseased component.

9. The method of claim 1, wherein the patient is a human being.

10. The method of claim 1, wherein measuring the level of the biomarkers comprises performing one or more methods including microarray analysis via fluorescence, chemiluminesence, or electrical signal detection, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), digital droplet PCR (ddPCR), solid-state nanopore detection, RNA switch activation, a Northern blot, or a serial analysis of gene expression (SAGE).

11. A method of diagnosing and treating a patient having inflammation, the method comprising:

a) measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in a biological sample of the patient; and

b) first analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, wherein increased levels of expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection; and

c) further analyzing the levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, HERC5, DDX60, HESX1, IFI6, MX1, OASL, LAX1, IFIT5, IFIT3, KCTD14, OAS2, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, RSAD2, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB to determine a bacterial or viral infection.

12. The method of claim 11, further comprising calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition.

13. The method of any of claims 11-12, further comprising calculating a bacterial/viral metascore for the patient if the patient is diagnosed as having an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

14. The method of claim 11, wherein the levels of the biomarkers are compared to time-matched reference values for infected or non-infected subjects.

15. The method of claim 11, wherein the non-infectious inflammatory condition is selected from the group consisting of systemic inflammatory response syndrome (SIRS), an autoimmune disorder, a traumatic injury, and surgery.

16. The method of claim 11, wherein the patient is a human being.

17. The method of claim 11, wherein measuring the levels of the biomarkers comprises performing one or more methods including microarray analysis via fluorescence, chemiluminesence, or electrical signal detection, polymerase chain reaction (PCR), reverse transcriptase polymerase chain reaction (RT-PCR), digital droplet PCR (ddPCR), solid-state nanopore detection, RNA switch activation, a Northern blot, or a serial analysis of gene expression (SAGE).

18. A kit comprising agents for measuring levels of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set

of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, DDX60, HESX1, OASL, LAX1, IFIT5, KCTD14, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB.

19. The kit of claim 18, further comprising agents for measuring the levels of CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers.

20. The kit of any of claims 18-19, further comprising a microarray.

21. The kit of claim 20, wherein the microarray comprises an oligonucleotide that hybridizes to an IFI27 polynucleotide, an oligonucleotide that hybridizes to a JUP polynucleotide, an oligonucleotide that hybridizes to a LAX1 polynucleotide, an oligonucleotide that hybridizes to a HK3 polynucleotide, an oligonucleotide that hybridizes to a TNIP1 polynucleotide, an oligonucleotide that hybridizes to a GPAA1 polynucleotide, and an oligonucleotide that hybridizes to a CTSB polynucleotide

22. The kit of claim 20, wherein the microarray further comprising an oligonucleotide that hybridizes to a CEACAM1 polynucleotide, an oligonucleotide that hybridizes to a ZDHHC19 polynucleotide, an oligonucleotide that hybridizes to a C9orf95 polynucleotide, an oligonucleotide that hybridizes to a GNA15 polynucleotide, an oligonucleotide that hybridizes to a BATF polynucleotide, an oligonucleotide that hybridizes to a C3AR1 polynucleotide, an oligonucleotide that hybridizes to a KIAA1370 polynucleotide, an oligonucleotide that hybridizes to a TGFBI polynucleotide, an oligonucleotide that hybridizes to a MTCH1 polynucleotide, an oligonucleotide that hybridizes to a RPGRIP1 polynucleotide, and an oligonucleotide that hybridizes to a HLA-DPB1 polynucleotide.

23. The kit of claim 18, further comprising information, in electronic or paper form, comprising instructions to correlate the detected levels of each biomarker with sepsis.

24. A computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps comprising:

a) receiving inputted patient data comprising values for levels of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, DDX60, HESX1, OASL, LAX1, IFIT5, KCTD14, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB biomarkers in the biological sample from the patient;

b) analyzing the level of each of the biomarkers and comparing with respective reference value ranges for the biomarkers;

c) calculating a bacterial/viral metascore for the patient based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and

d) displaying information regarding the diagnosis of the patient.

25. The method of claim 24, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

26. A diagnostic system for performing the method of claim 24, comprising:

a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein;

b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage

component in order to receive patient data and analyze patient data according to one or more algorithms; and

c) a display component for displaying information regarding the diagnosis of the patient.

27. The diagnostic system of claim 26, wherein the storage component comprises instructions for calculating the bacterial/viral metascore.

28. A computer implemented method for diagnosing a patient having inflammation, the computer performing steps comprising:

a) receiving inputted patient data comprising values for the levels of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in a biological sample from the patient;

b) analyzing the levels of each of the biomarkers and comparing with respective reference value ranges for the biomarkers;

c) calculating a sepsis metascore for the patient, wherein a sepsis metascore that is higher than the reference value ranges for a non-infected control subject indicates that the patient has an infection, and a sepsis metascore that is within the reference value ranges for a non-infected control subject indicates that the patient has a non-infectious inflammatory condition;

d) calculating a bacterial/viral metascore for the patient if the sepsis metascore indicates that the patient has an infection, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection; and

e) displaying information regarding the diagnosis of the patient.

29. The method of claim 28, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

30. A diagnostic system for performing the method of claim 28, comprising:

AMENDED SHEET (ARTICLE 19)

a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein;

b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and

c) a display component for displaying information regarding the diagnosis of the patient.

31. The diagnostic system of claim 30, wherein the storage component comprises instructions for calculating the sepsis metascore and the bacterial/viral metascore.

32. A method for diagnosing and treating an infection in a patient, the method comprising:

a) obtaining a biological sample from the patient;

b) measuring the levels of expression of any set of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection; wherein the first set of biomarkers comprise at least one of TSPO, EMR1, NINJ2, ACPP, TBXAS1, PGD, S100A12, SORT1, TNIP1, RAB31, SLC12A9, PLP2, IMPA2, GPAA1, LTA4H, RTN3, CETP, TALD01, HK3, ACAA1, CAT, DOK3, SORL1, PYGL, DYSF, TWF2, TKT, CTSB, FLII, PROS1, NRD1, STAT5B, CYBRD1, PTAFR, and LAPTM5; and wherein the second set of biomarkers comprise at least one of OAS1, IFIT1, SAMD9, ISG15, DDX60, HESX1, OASL, LAX1, IFIT5, KCTD14, RTP4, PARP12, LY6E, ADA, IFI44L, IFI27, IFI44, OAS3, IFIH1, SIGLEC1, JUP, STAT1, CUL1, DNMT1, IFIT2, CHST12, ISG20, DHX58, EIF2AK2, XAF1, and GZMB; and

c) analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for a noninfected control subject, wherein differential expression of the viral response genes compared to the reference value ranges for a noninfected control subject indicate that the patient has a viral infection, and differential expression of the

bacterial response genes compared to the reference value ranges for a noninfected control subject indicate that the patient has a bacterial infection.

33. The method of claim 32, wherein the set of viral and bacterial response genes are selected from the group consisting of:

a) a set of viral response genes comprising OAS2 and CUL1 and a set of bacterial response genes comprising SLC12A9, ACPP, STAT5B;

b) a set of viral response genes comprising ISG15 and CHST12 and a set of bacterial response genes comprising EMR1 and FLII;

c) a set of viral response genes comprising IFIT1, SIGLEC1, and ADA and a set of bacterial response genes comprising PTAFR, NRD1, PLP2;

d) a set of viral response genes comprising MX1 and a set of bacterial response genes comprising DYSF, TWF2;

e) a set of viral response genes comprising RSAD2 and a set of bacterial response genes comprising SORT1 and TSPO;

f) a set of viral response genes comprising IFI44L, GZMB, and KCTD14 and a set of bacterial response genes comprising TBXAS1, ACAA1, and S100A12;

g) a set of viral response genes comprising LY6E and a set of bacterial response genes comprising PGD and LAPTM5;

h) a set of viral response genes comprising IFI44, HESX1, and OASL and a set of bacterial response genes comprising NINJ2, DOK3, SORL1, and RAB31;

i) a set of viral response genes comprising OAS1 and a set of bacterial response genes comprising IMPA2 and LTA4H.

34. The method of any of claims 32-33, wherein the biological sample comprises whole blood or peripheral blood mononucleated cells (PBMCS).

35. The method of claim 32, wherein the levels of the biomarkers are compared to time-matched reference values for infected or non-infected subjects.

36. The method of claim 32, further comprising calculating a bacterial/viral metascore for the patient t based on the levels of the biomarkers, wherein a positive bacterial/viral metascore for the patient indicates that the patient has a viral infection and a negative bacterial/viral metascore for the patient indicates that the patient has a bacterial infection.

37. The method of claim 32, further comprising measuring levels of expression of IFI27, JUP, LAX1, HK3, TNIP1, GPAA1, CTSB, CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers in the biological sample; and analyzing the levels of expression of each biomarker in conjunction with respective reference value ranges for the biomarkers, wherein increased levels of expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, and C3AR1 biomarkers and decreased levels of expression of the KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared to the reference value ranges for the biomarkers for a non-infected control subject indicate that the patient has an infection, and absence of differential expression of the CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, and HLA-DPB1 biomarkers compared the non-infected control subject indicates that the patient does not have an infection.

38. A kit comprising agents for measuring the levels of expression of a set of viral response genes and a set of bacterial response genes selected from the group consisting of:

a) a set of viral response genes comprising OAS2 and CUL1 and a set of bacterial response genes comprising SLC12A9, ACPP, STAT5B;

b) a set of viral response genes comprising ISG15 and CHST12 and a set of bacterial response genes comprising EMR1 and FLII;

c) a set of viral response genes comprising IFIT1, SIGLEC1, and ADA and a set of bacterial response genes comprising PTAFR, NRD1, PLP2;

d) a set of viral response genes comprising MX1 and a set of bacterial response genes comprising DYSF, TWF2;

e) a set of viral response genes comprising RSAD2 and a set of bacterial response genes comprising SORT1 and TSPO;

f) a set of viral response genes comprising IFI44L, GZMB, and KCTD14 and a set of bacterial response genes comprising TBXAS1, ACAA1, and S100A12;

g) a set of viral response genes comprising LY6E and a set of bacterial response genes comprising PGD and LAPTM5;

h) a set of viral response genes comprising IFI44, HESX1, and OASL and a set of bacterial response genes comprising NINJ2, DOK3, SORL1, and RAB31; and

i) a set of viral response genes comprising OAS1 and a set of bacterial response genes comprising IMPA2 and LTA4H.

39. The kit of claim 38, further comprising a microarray.

40. A computer implemented method for diagnosing a patient suspected of having an infection, the computer performing steps comprising:

a) receiving inputted patient data comprising values for the levels of expression of at least two biomarkers in a biological sample of a patient; the at least two biomarkers selected from either or both of a first set of biomarkers wherein a higher level of expression indicates a bacterial infection, and a second set of biomarkers wherein a higher level of expression indicates a viral infection, wherein the set of viral response genes comprises one or more genes selected from the group consisting of CUL1, ISG15, CHST12, IFIT1, SIGLEC1, ADA, IFI44L, GZMB, KCTD14, LY6E, IFI44, HESX1, OASL, OAS1, OAS3, EIF2AK2, DDX60, DNMT1, IFIH1, SAMD9, IFIT5, XAF1, ISG20, PARP12, IFIT2, DHX58, STAT1, and the set of bacterial response genes comprises one or more genes selected from the group consisting of SLC12A9, ACPP, STAT5B, EMR1, FLII, PTAFR, NRD1, PLP2, DYSF, TWF2, SORT1, TSPO, TBXAS1, ACAA1, S100A12, PGD, LAPTM5, NINJ2, DOK3, SORL1, RAB31, IMPA2, LTA4H, TALDO1, TKT, PYGL, CETP, PROS1, RTN3, CAT, CYBRD1;

b) analyzing the levels of expression of the set of viral response genes and the set of bacterial response genes and comparing with respective reference value ranges for a noninfected control subject;

c) calculating a bacterial/viral metascore for the patient based on the levels of expression of the set of viral response genes and the set of bacterial response genes; and

d) displaying information regarding the diagnosis of the patient.

41. A diagnostic system for performing the method of claim 40, comprising:

a) a storage component for storing data, wherein the storage component has instructions for determining the diagnosis of the patient stored therein;

b) a computer processor for processing data, wherein the computer processor is coupled to the storage component and configured to execute the instructions stored in the storage component in order to receive patient data and analyze patient data according to one or more algorithms; and

c) a display component for displaying information regarding the diagnosis of the patient.

42. The method of claim 1, wherein measuring the level of expression of the biomarkers comprises measuring an amount of mRNA, or polynucleotides derived therefrom, present in a biological sample for each of the at least two biomarkers.

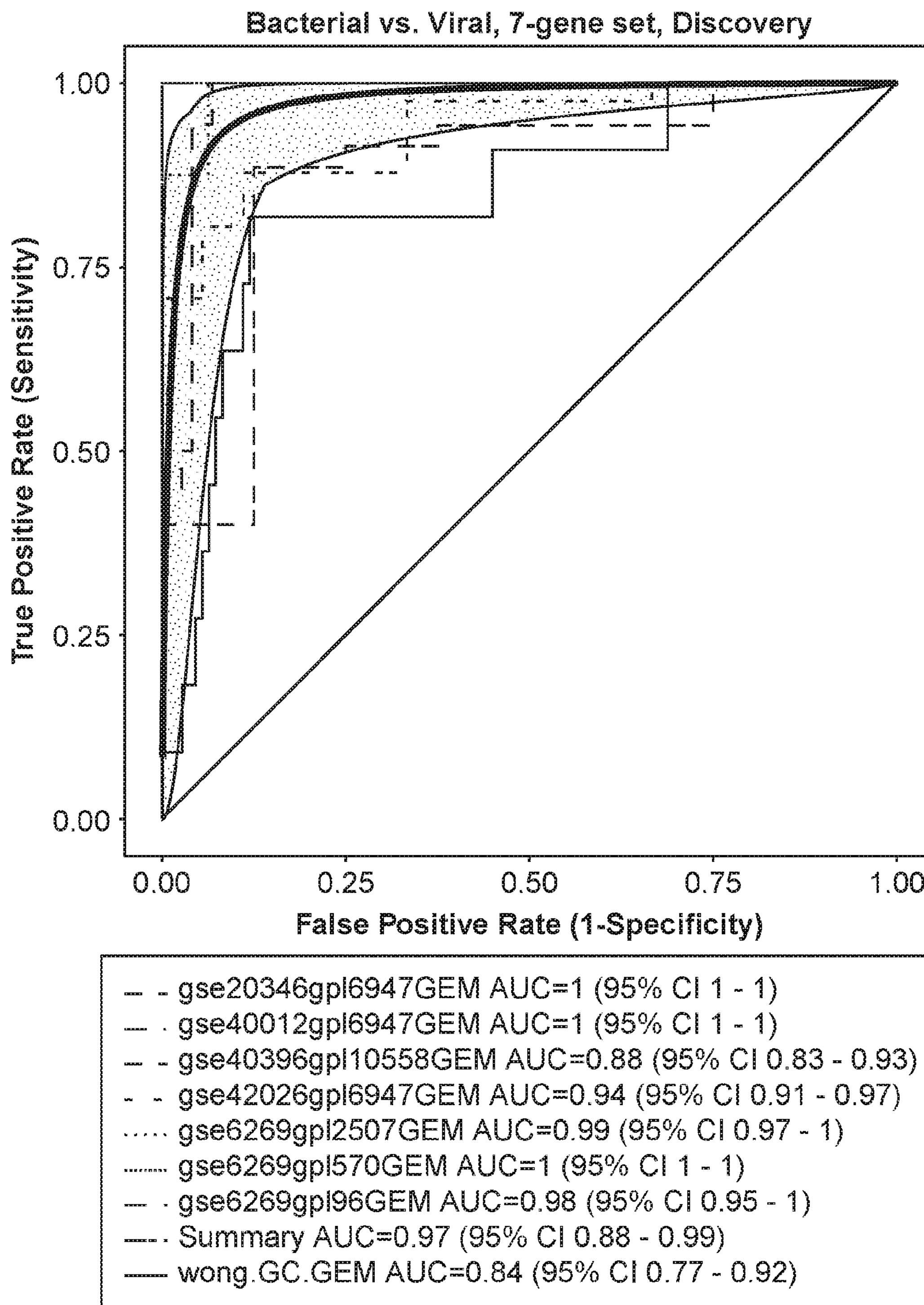


FIG. 1A

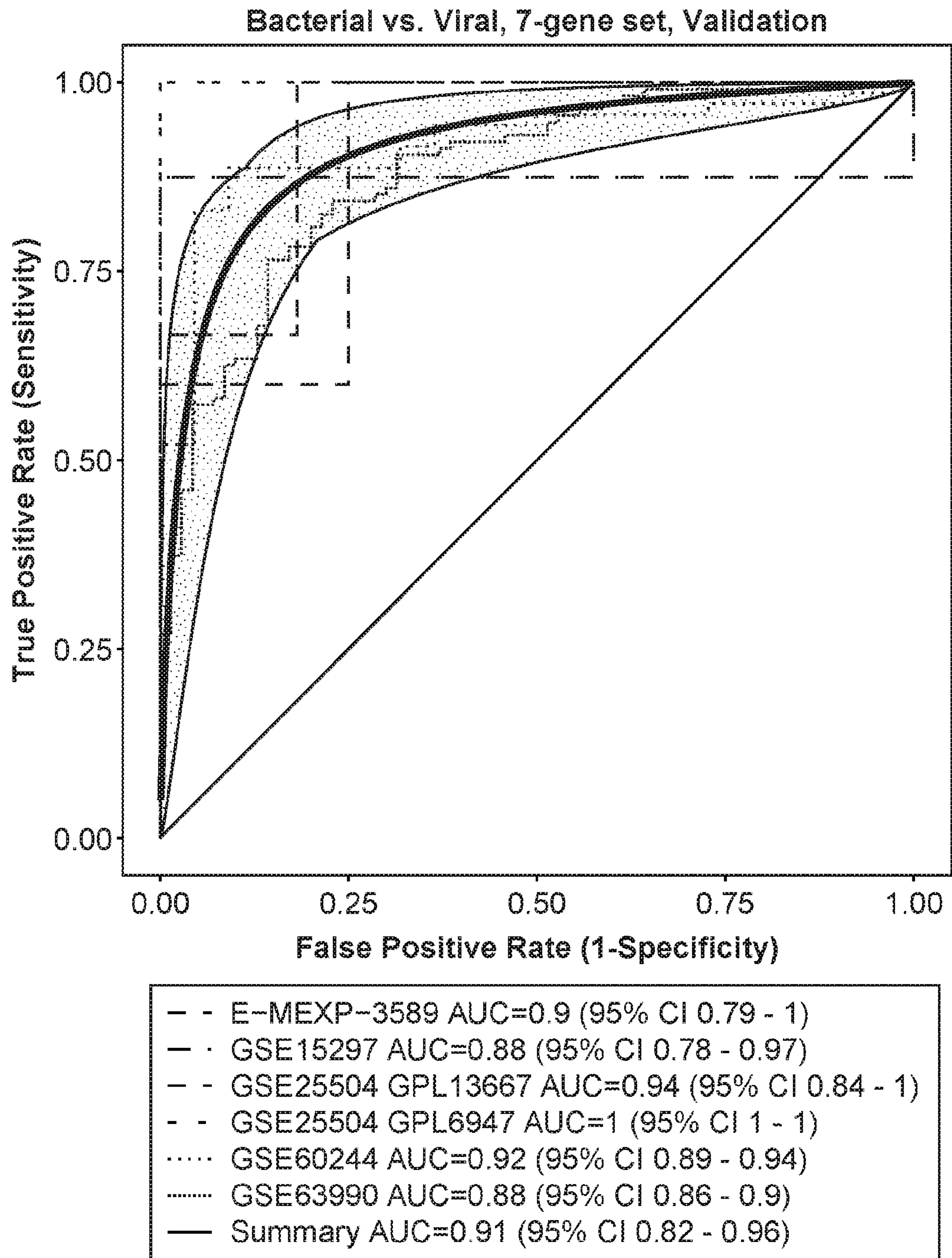


FIG. 1B

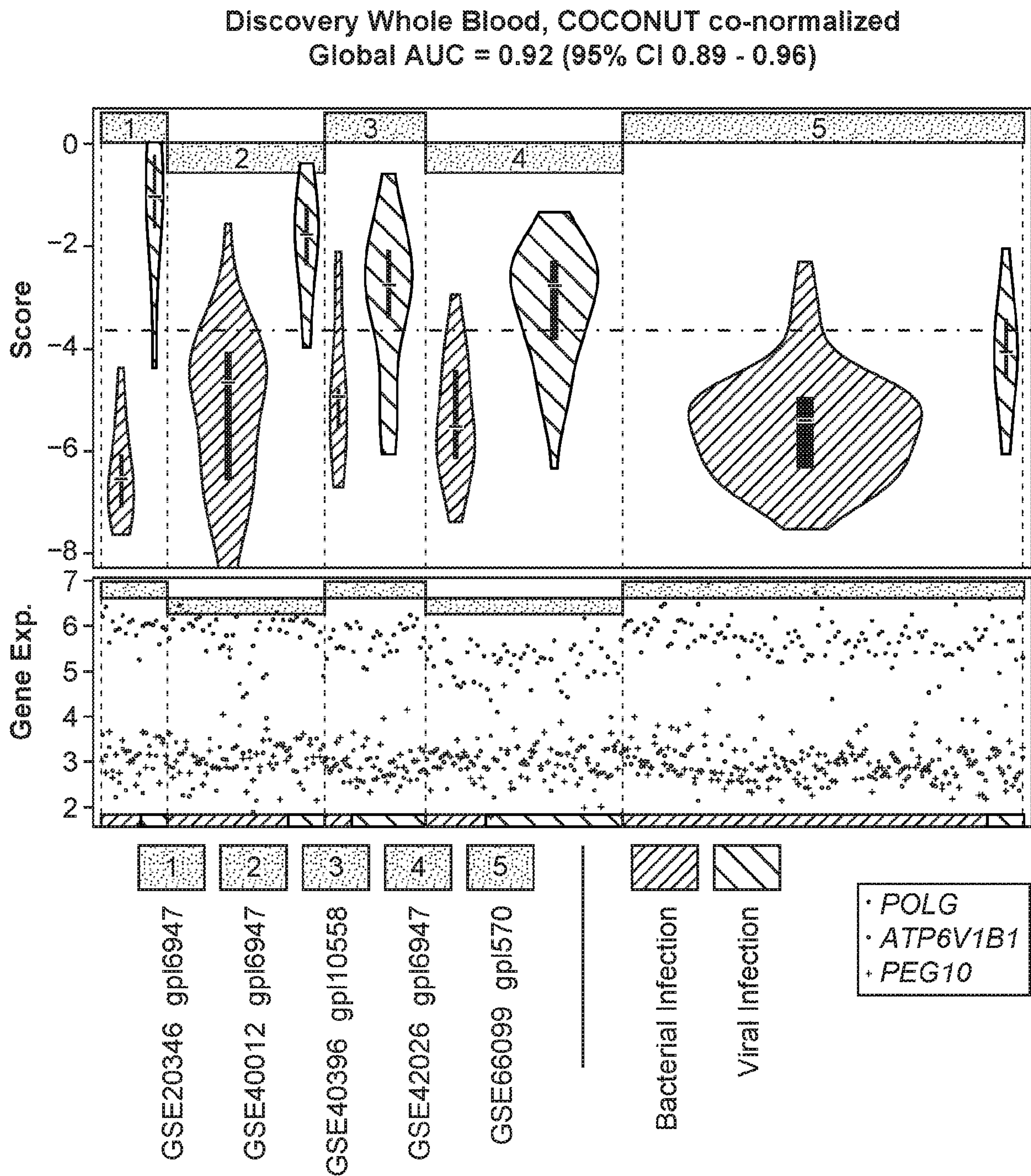


FIG. 2

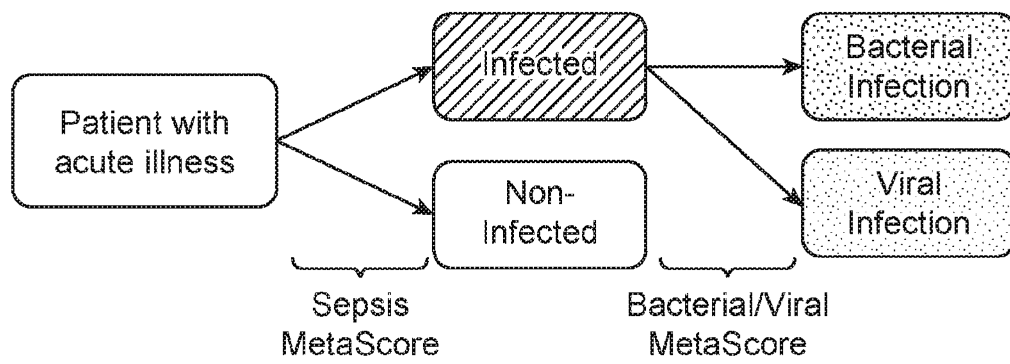


FIG. 3A

SUBSTITUTE SHEET (RULE 26)

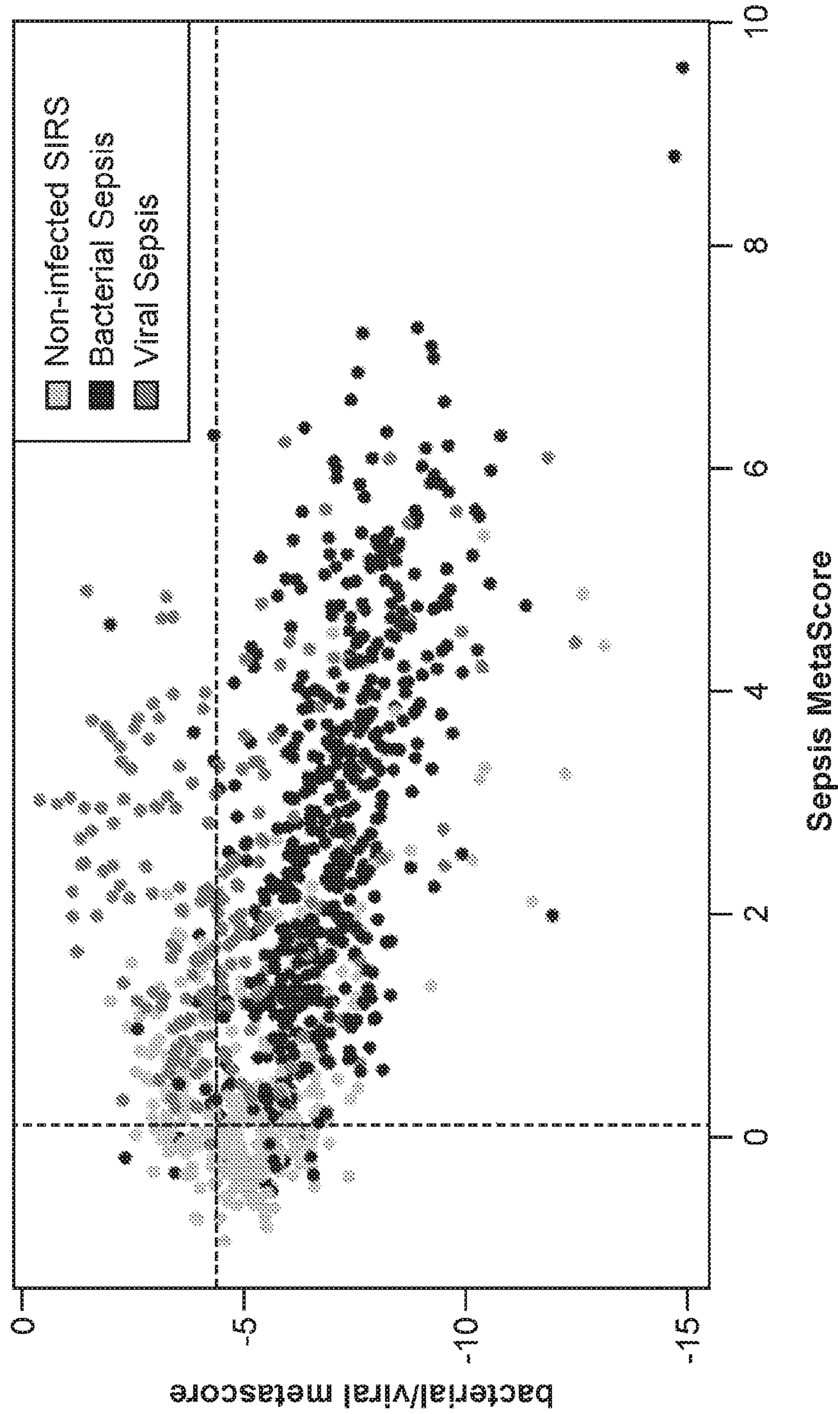


FIG. 3B

		Predicted		
		Non-infected	bacterial	viral
Ground Truth	Non-infected	137	115	67
	bacterial	19	504	13
	viral	1	94	107

FIG. 3C

Organism Type	Count
Bacillus sp.	1
Bacteroides	1
E. coli	6
Enterobacter cloacae	3
Enterococcus faecalis	2
Gram negative rods	5
Gram positive cocci	1
Group A streptococcus	2
Group B streptococcus	3
H. influenzae	1
Klebsiella oxytoca	1
Klebsiella pneumoniae	6
Moraxella catarrhalis	2
Neisseria meningitidis	3
Pneumococcus	4
Pseudomonas	3
Staph aureus	5
Enterovirus	1
Metapneumovirus	1
Influenza A	4
Influenza A (H1N1)	1
Respiratory syncytial virus	1
Rhinovirus	1
West Nile Virus	1

FIG. 4A

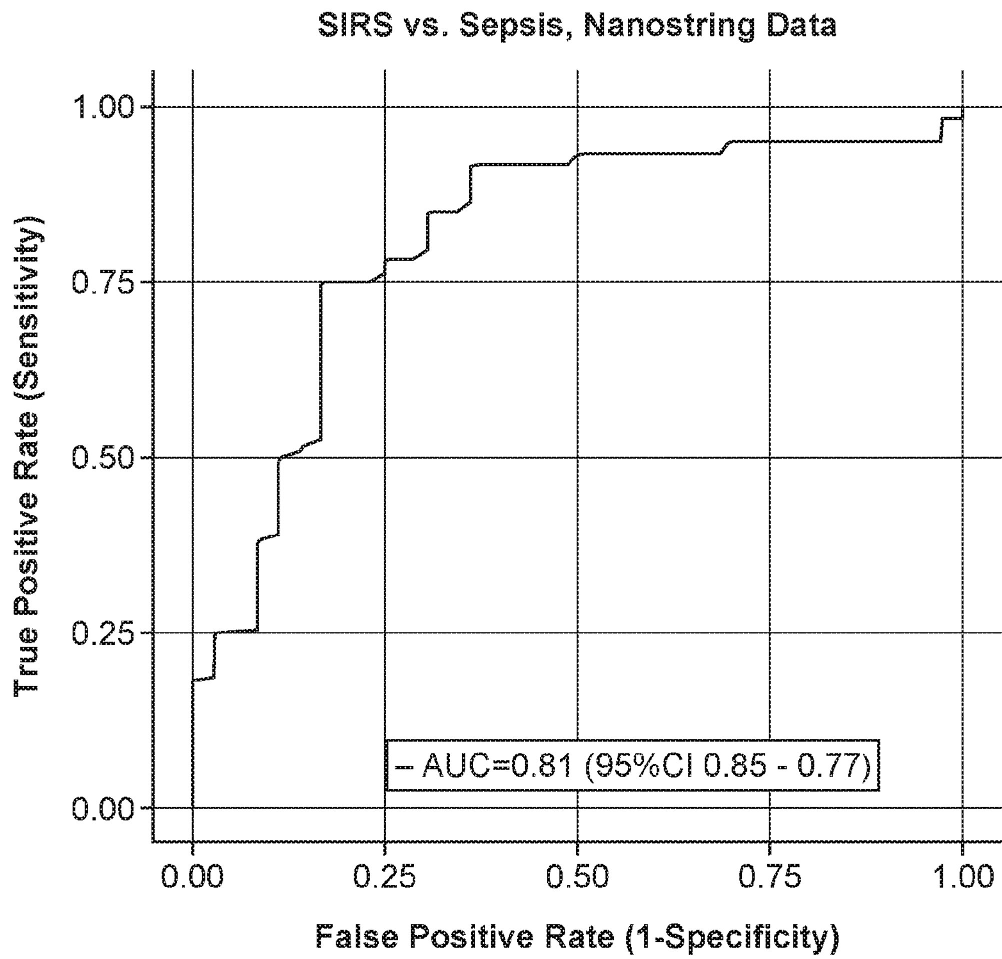


FIG. 4B

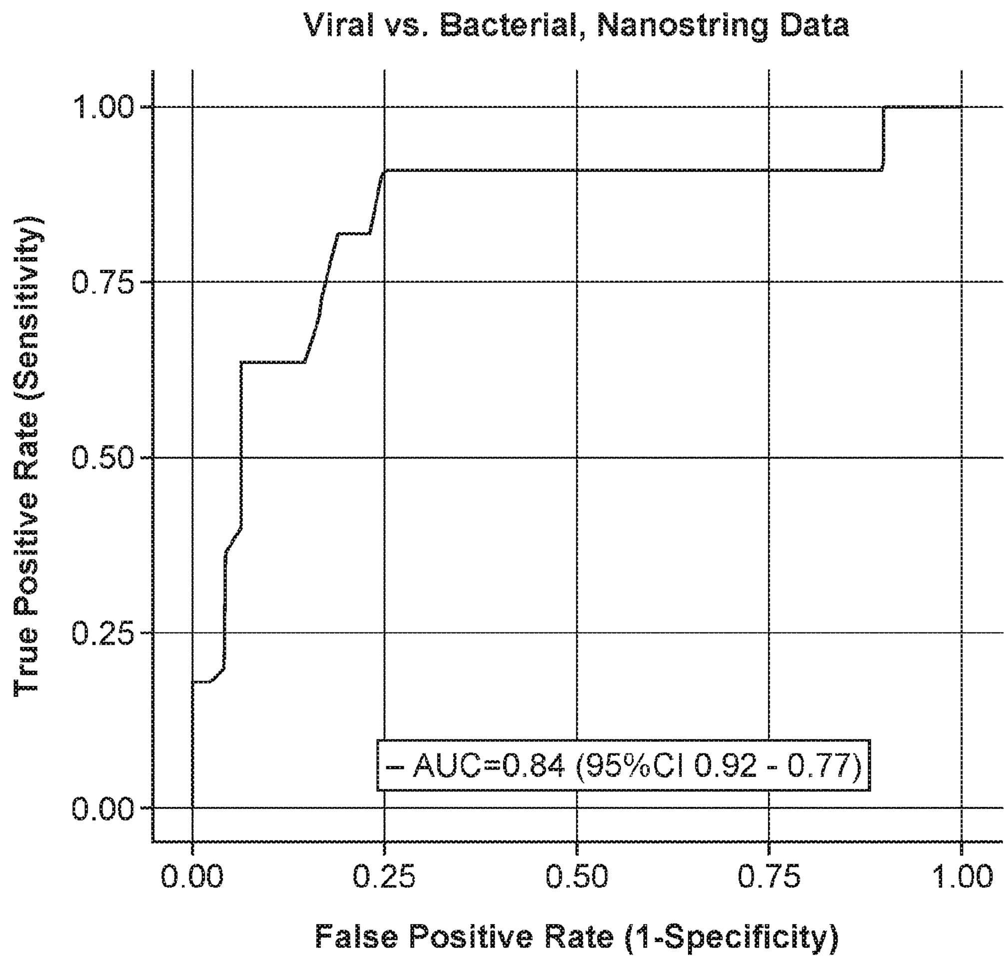


FIG. 4C

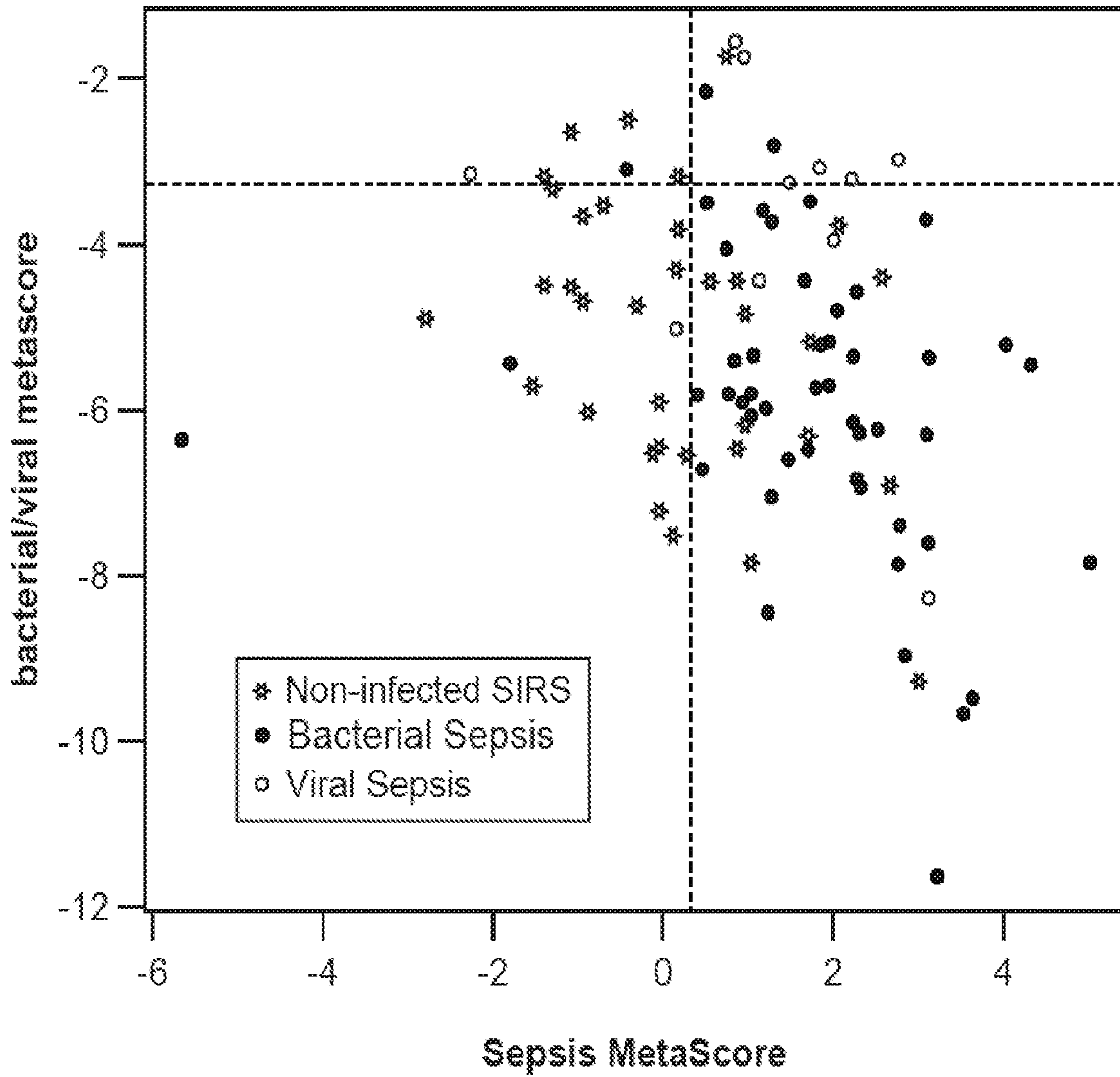


FIG. 4D

SUBSTITUTE SHEET (RULE 26)

		Predicted		
		Non-infected	bact	viral
Ground Truth	Non-infected	22	13	1
	bact	3	44	2
	viral	2	3	6

FIG. 4E

SUBSTITUTE SHEET (RULE 26)

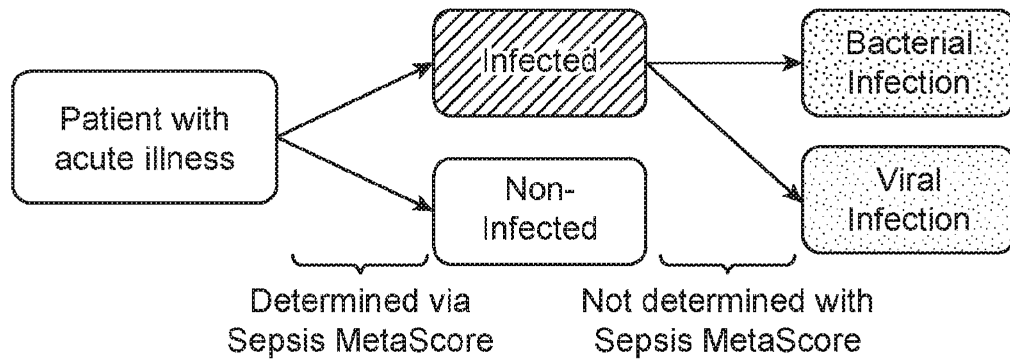


FIG. 5A

	N bacterial	N viral	Mean SMS Bacterial	Mean SMS Viral	Wilcoxon W Statistic	Wilcoxon P.value
EMEXP3589	4	5	0.372	-0.298	14	0.413
GSE15297	5	8	0.208	-0.13	21	0.943
GSE20346	12	8	-0.0292	0.0438	43	0.734
GSE25504 gpl13667	11	3	0.37	-1.36	32	**0.011**
GSE25504 gpl6947	26	1	0.0888	-2.31	26	0.0741
GSE40012	36	11	0.0348	-0.114	192	0.892
GSE40396	8	22	0.182	-0.0661	95	0.765
GSE42026	18	41	0.531	-0.233	536	**0.00537**
GSE60244	22	71	0.188	-0.0583	901	0.28
GSE63990	70	115	0.662	-0.403	6410	**1.59E-11**
GSE66099	109	11	0.0595	-0.59	792	0.0808

FIG. 5B

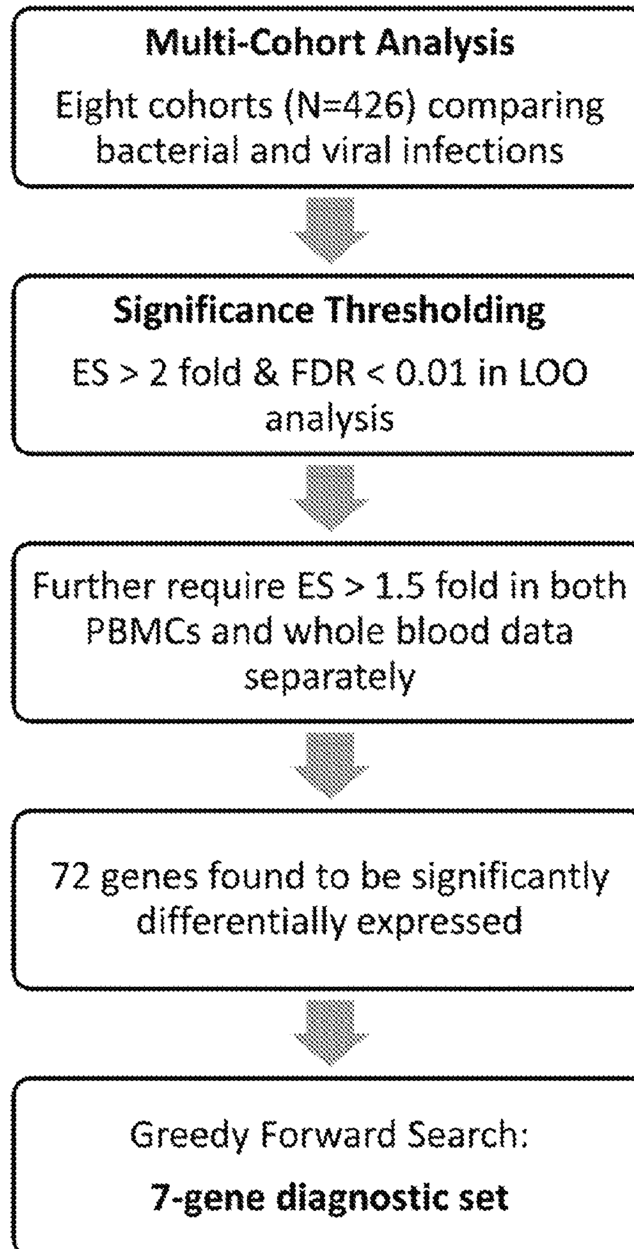
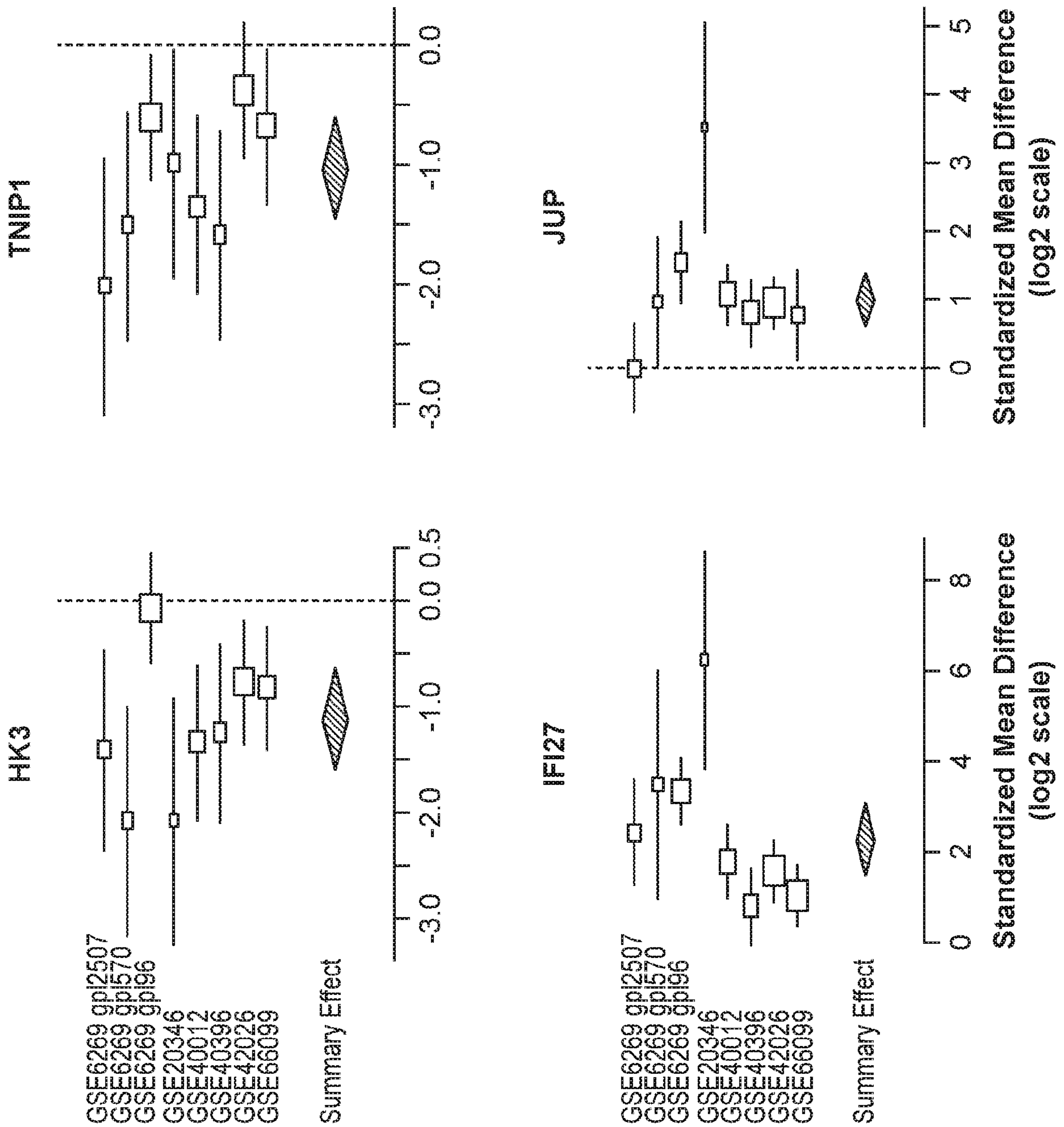
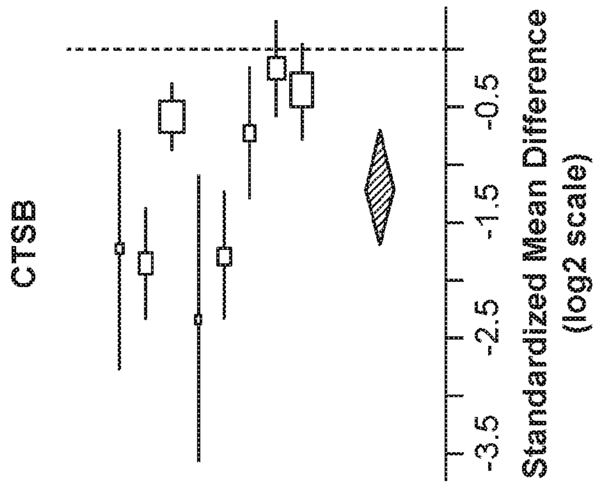
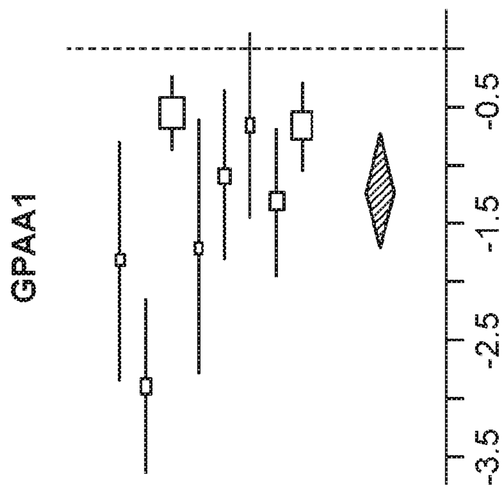


FIG. 6

FIG. 7







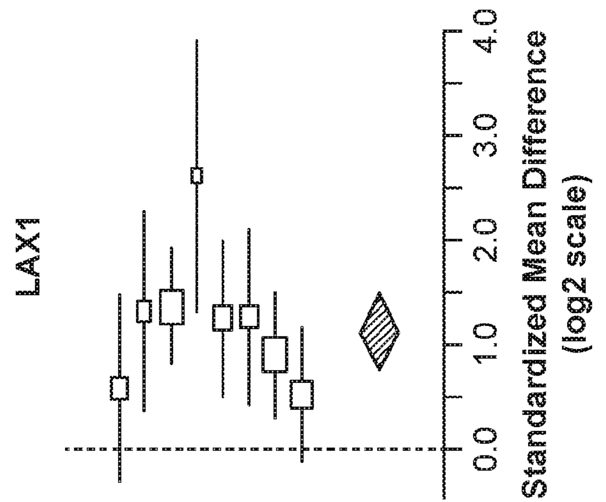


FIG. 7 (Cont.)

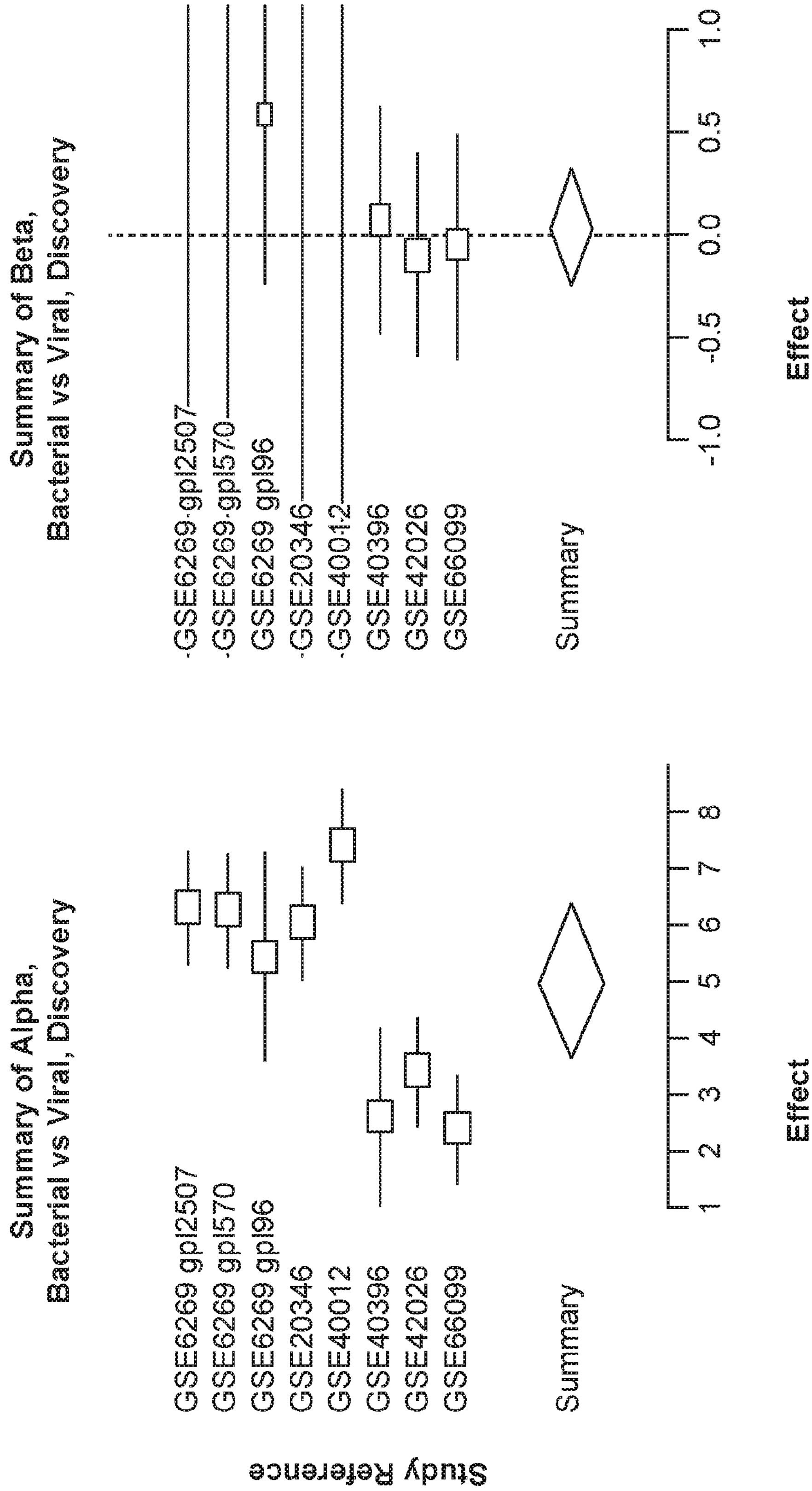


FIG. 8

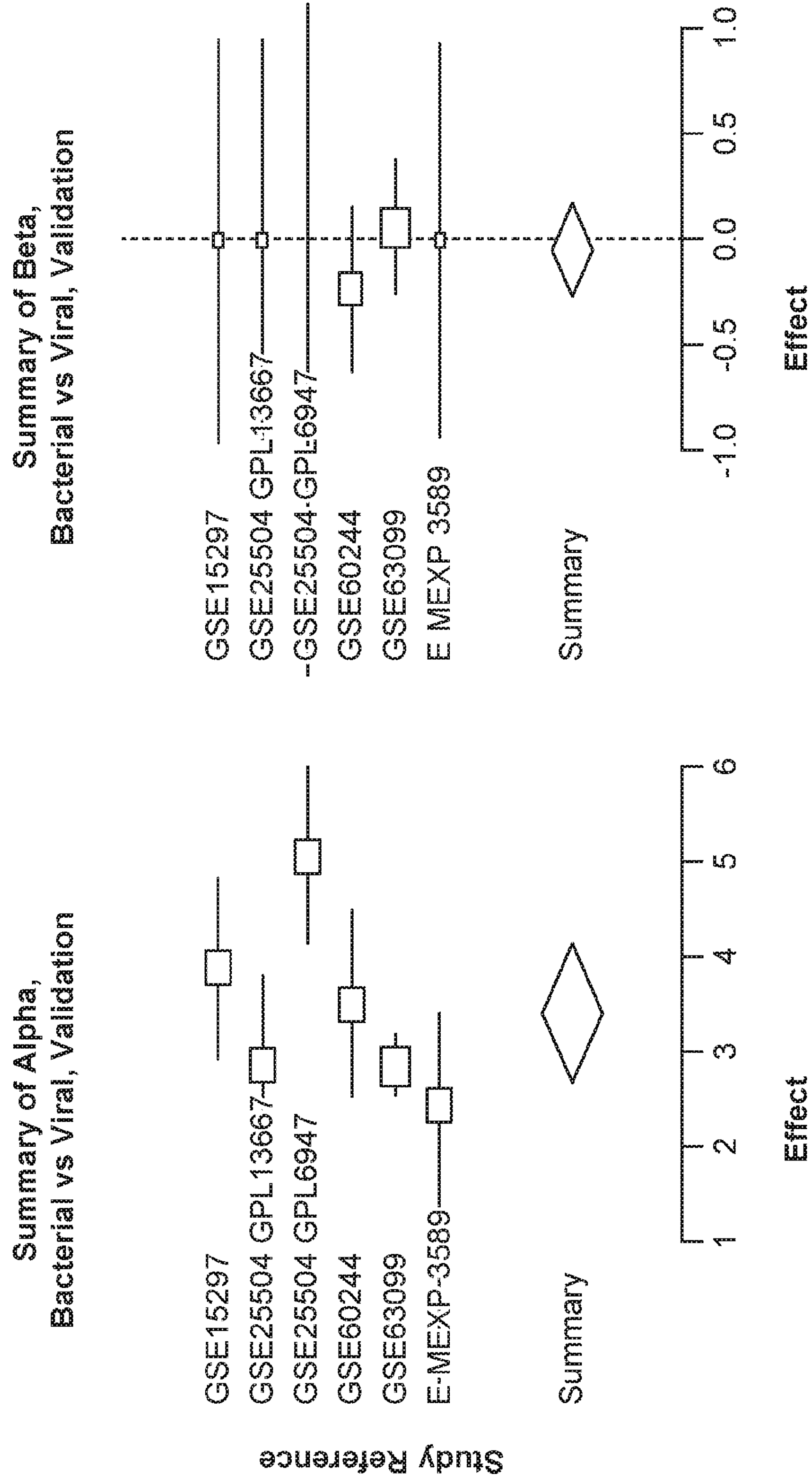


FIG. 9

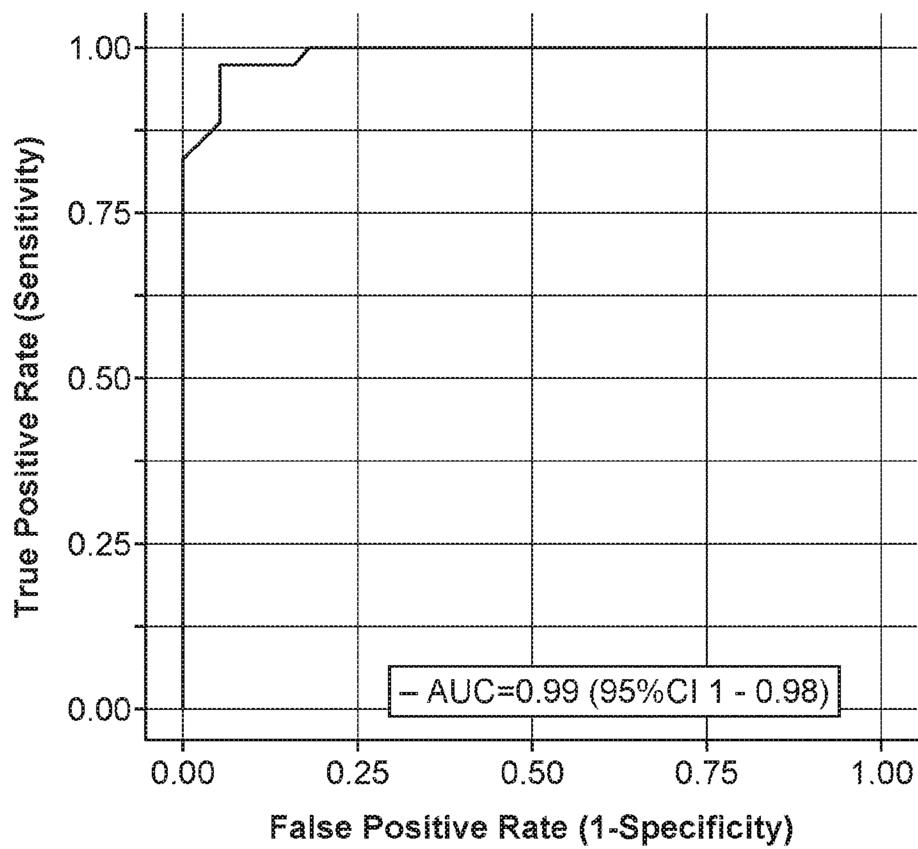


FIG. 10

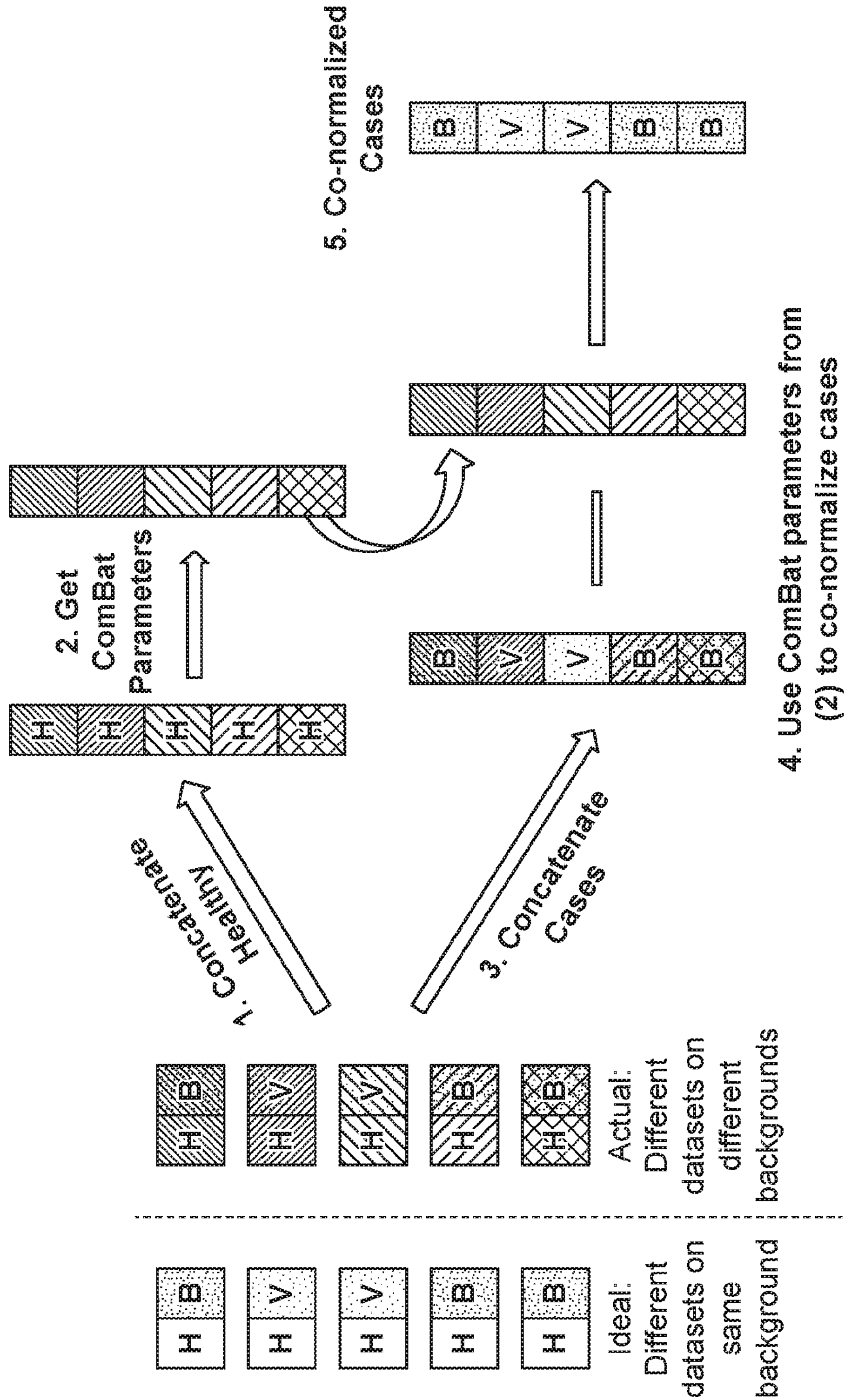


FIG. 11

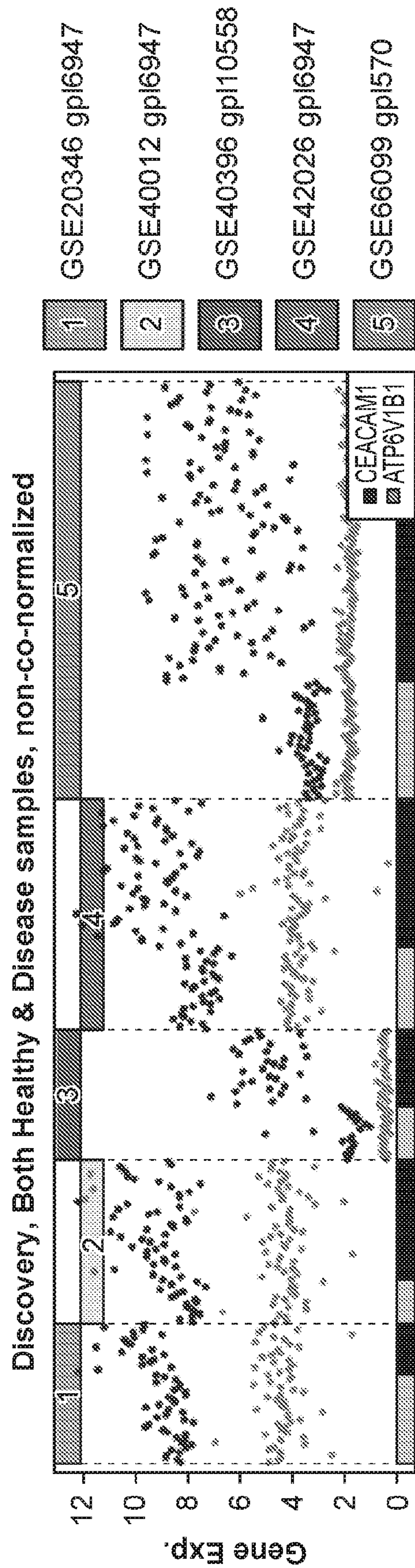


FIG. 12A

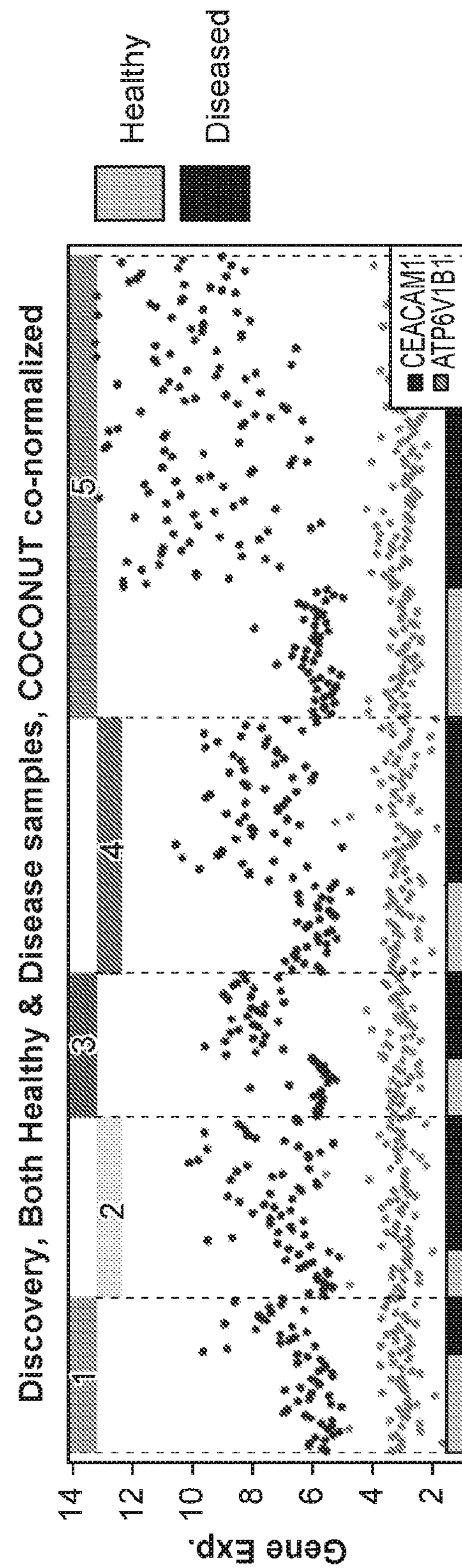


FIG. 12B

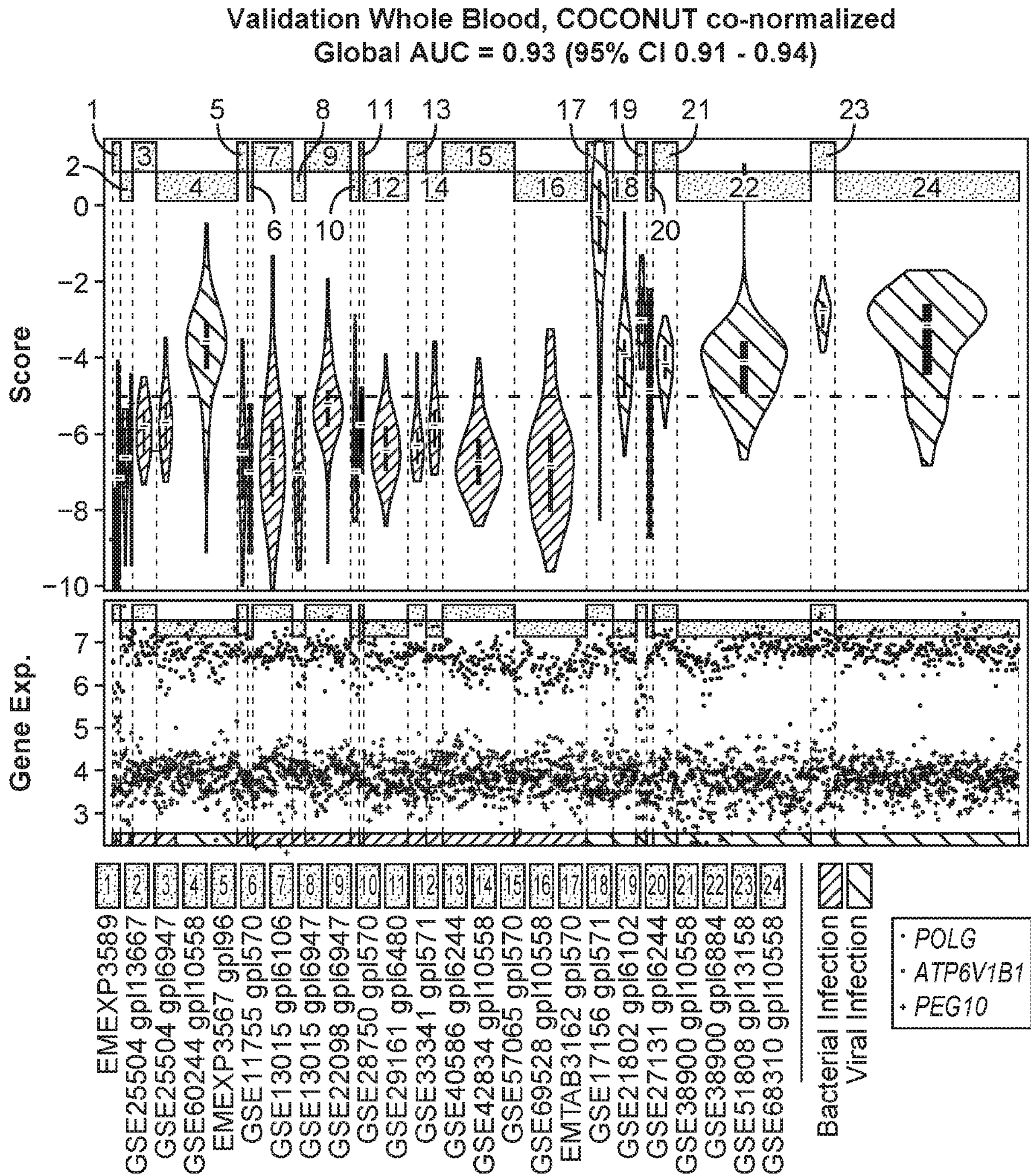


FIG. 13

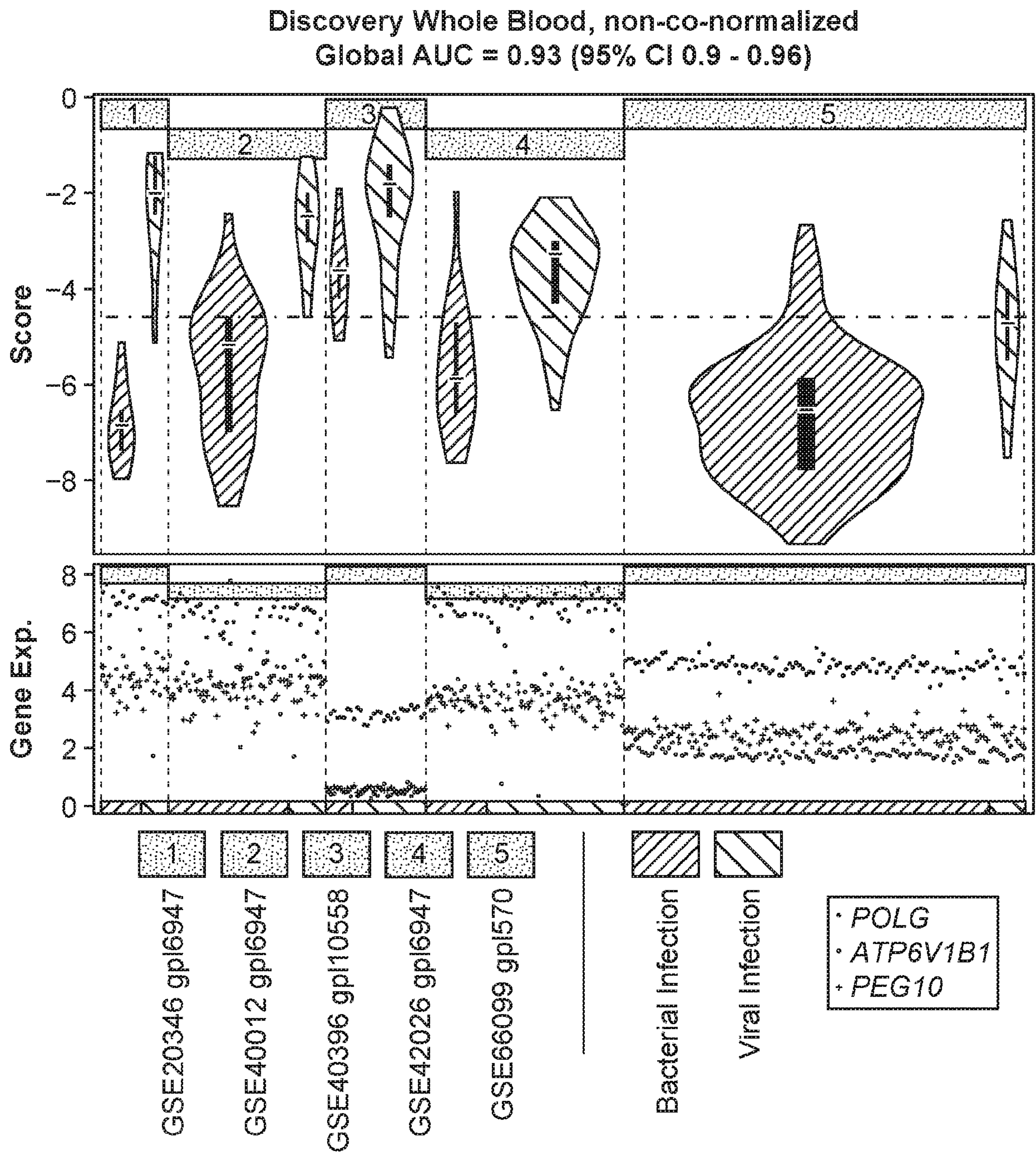


FIG. 14

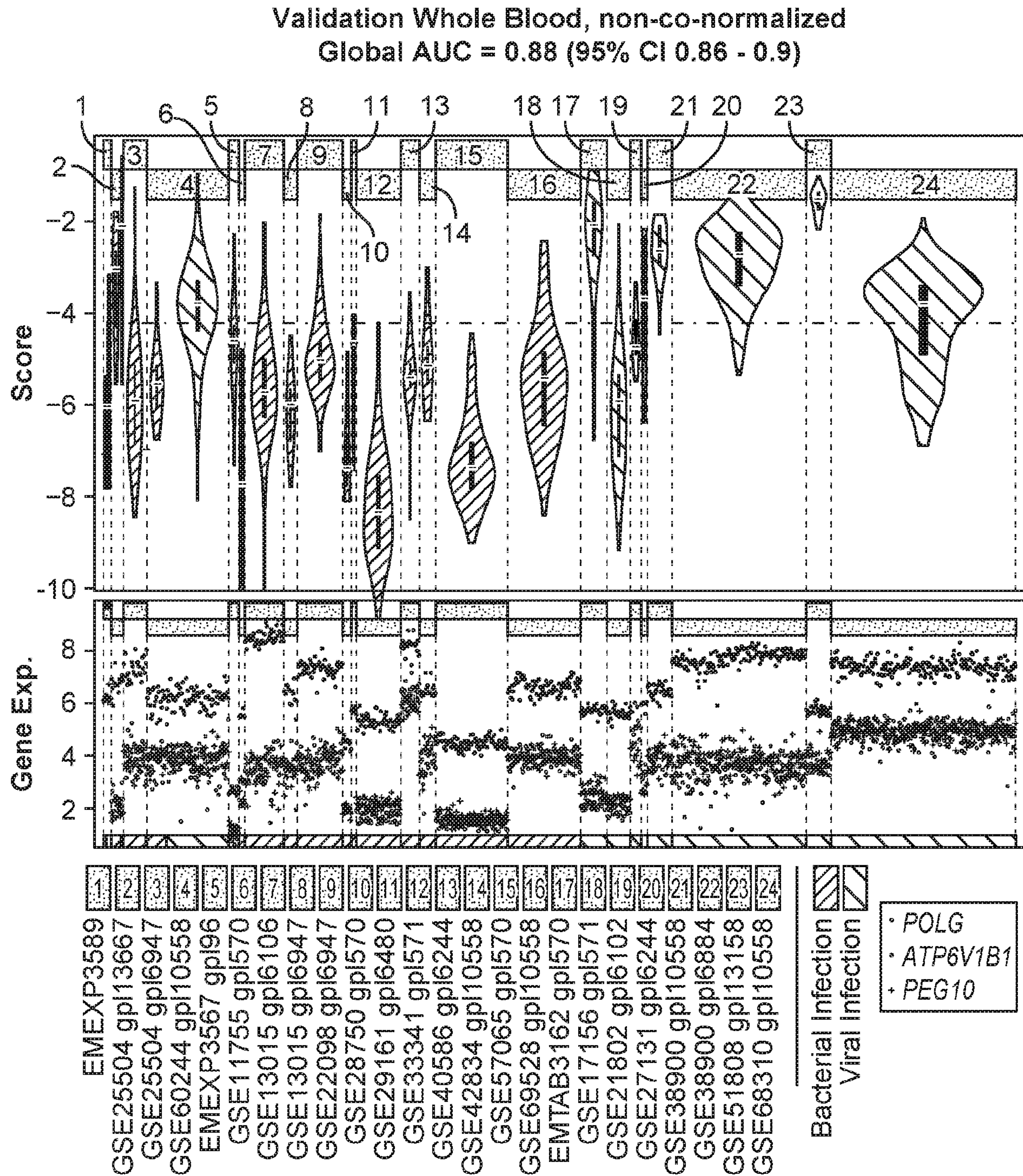


FIG. 15

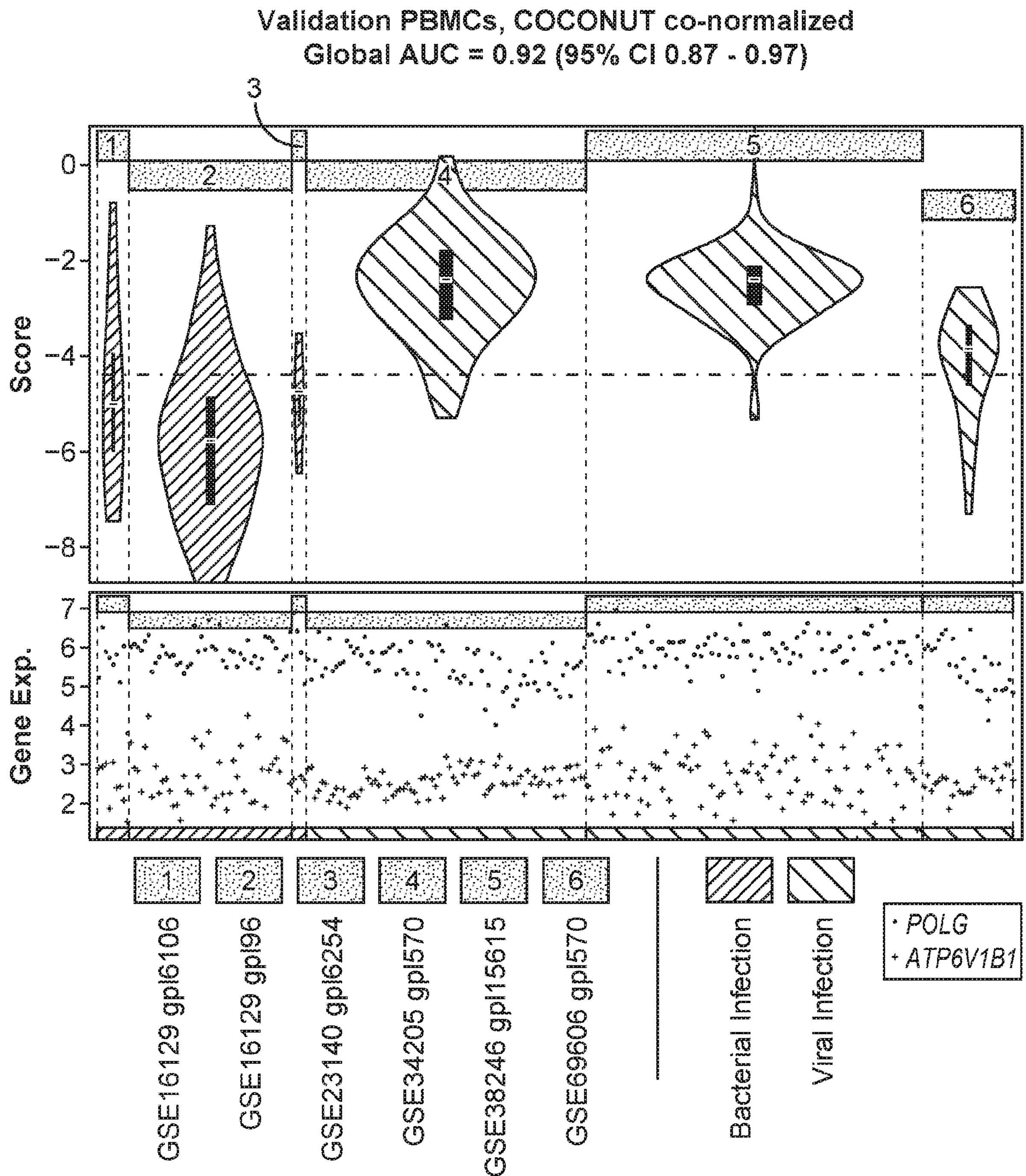


FIG. 16

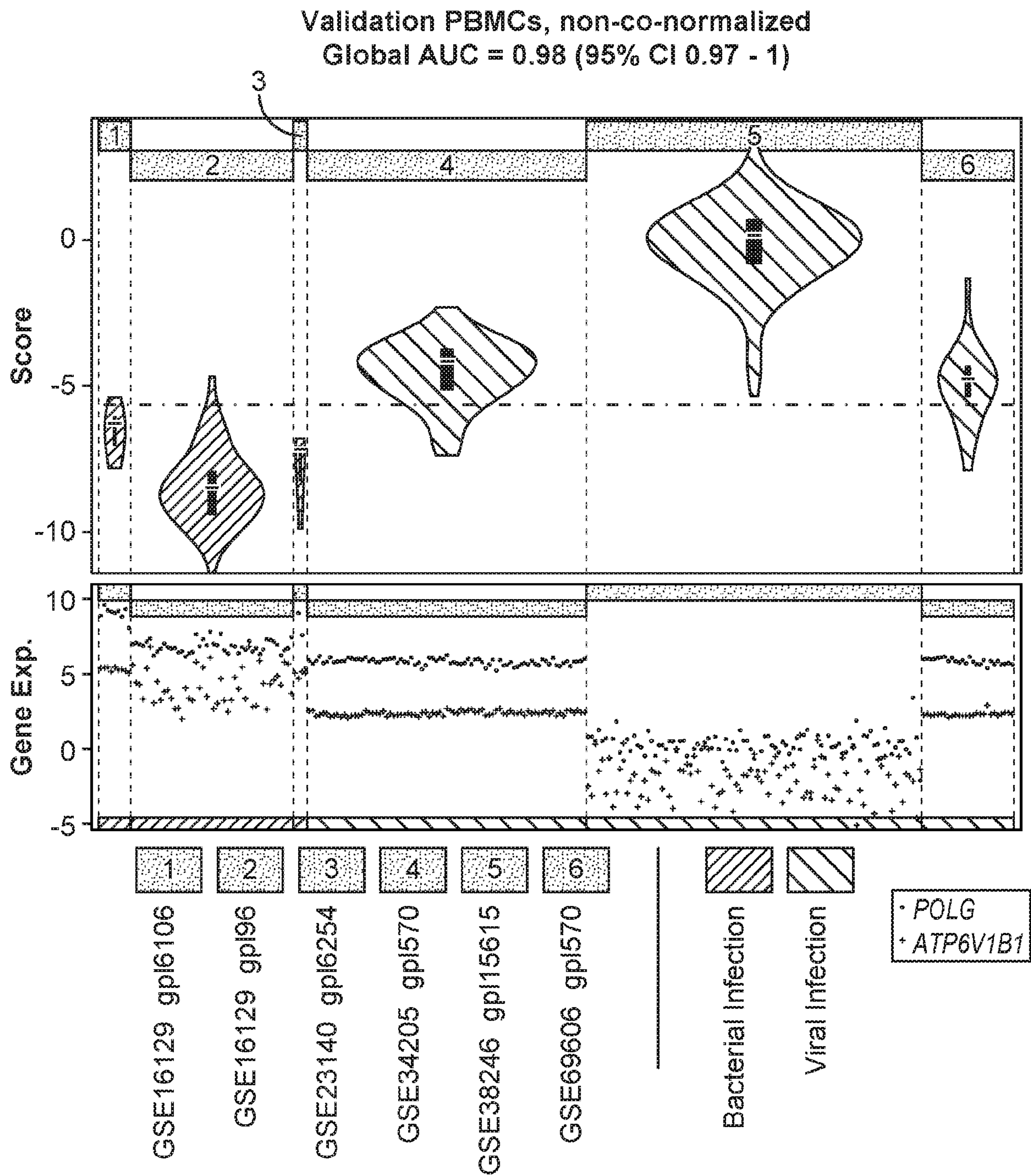


FIG. 17

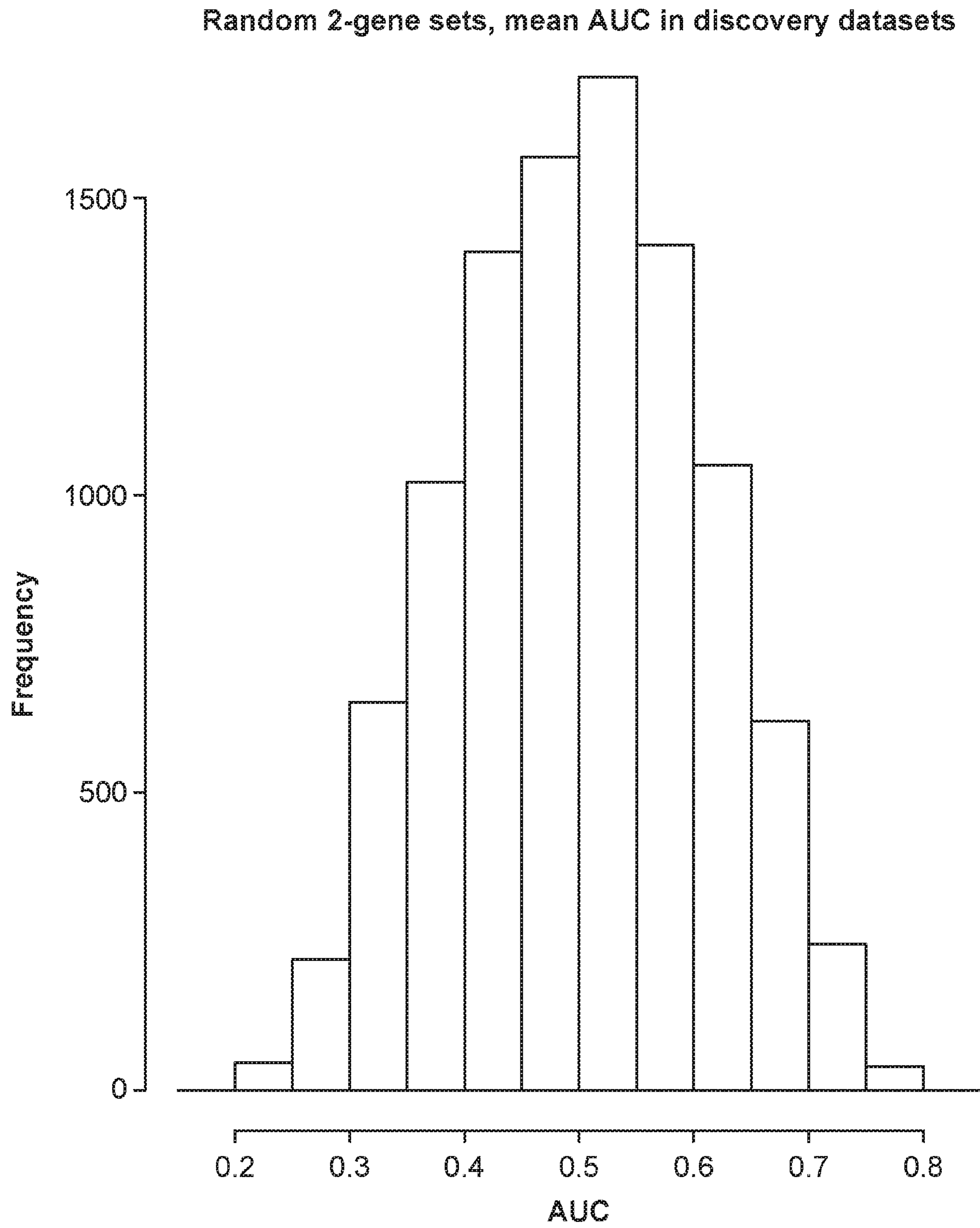


FIG. 18

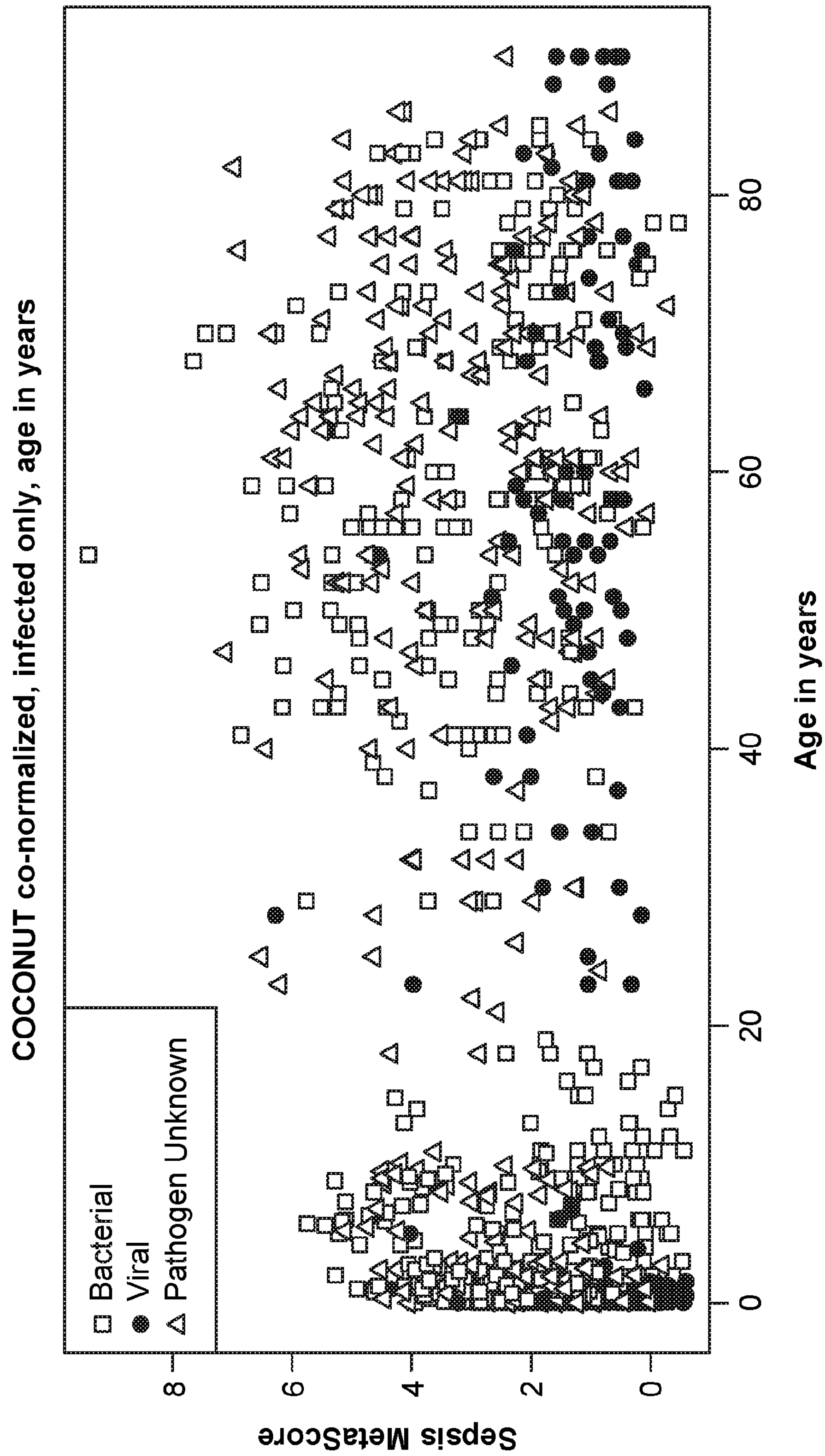


FIG. 19A

SUBSTITUTE SHEET (RULE 26)

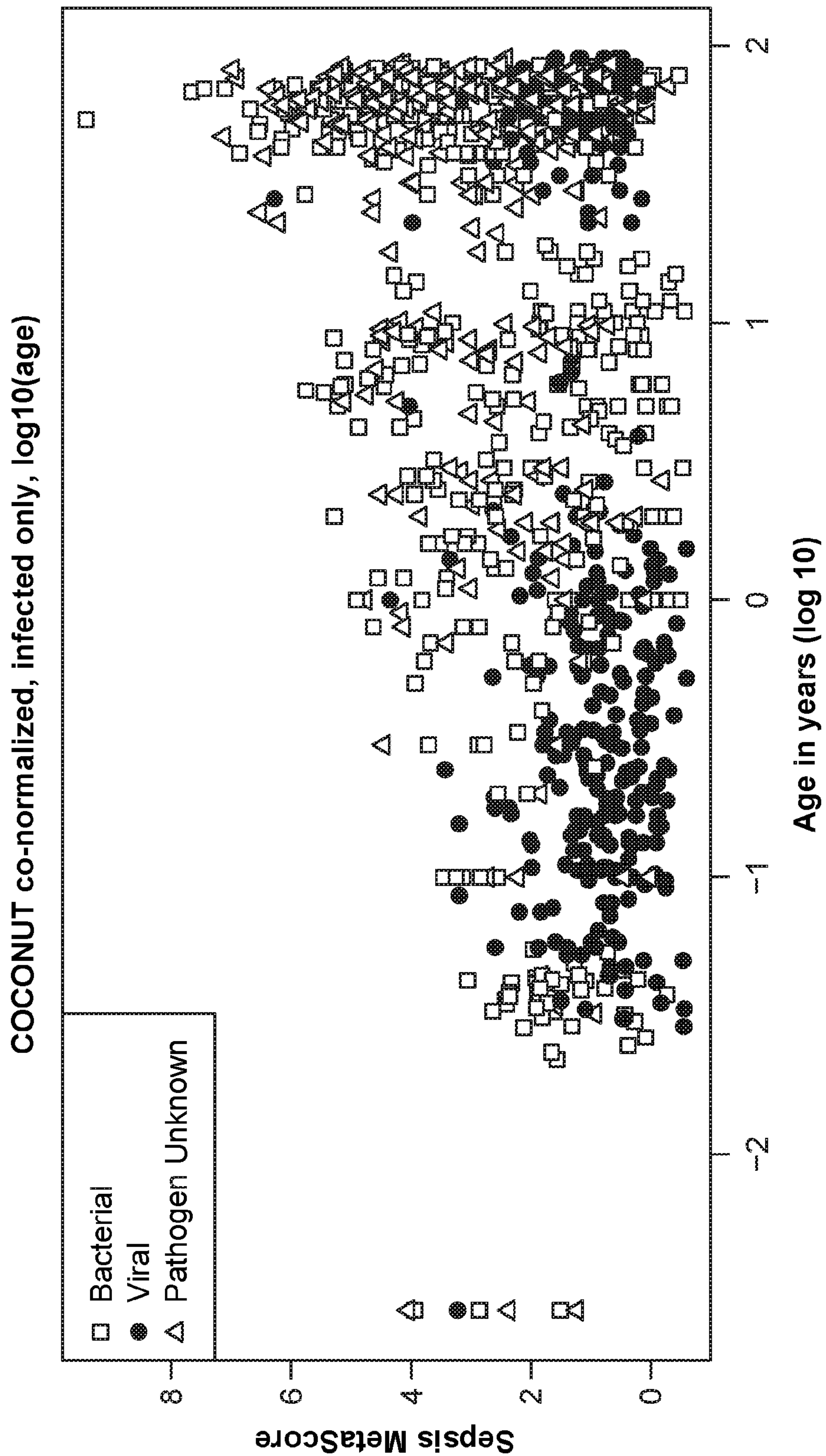


FIG. 19B

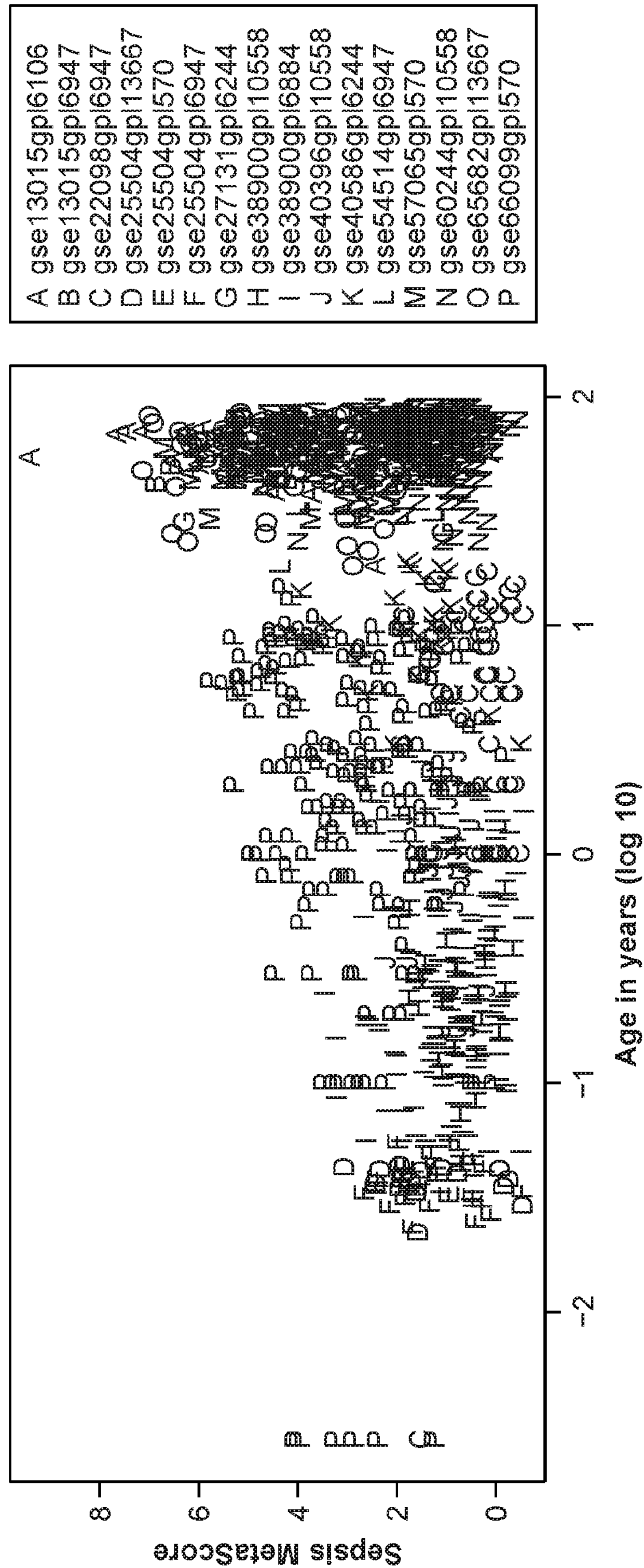


FIG. 19C

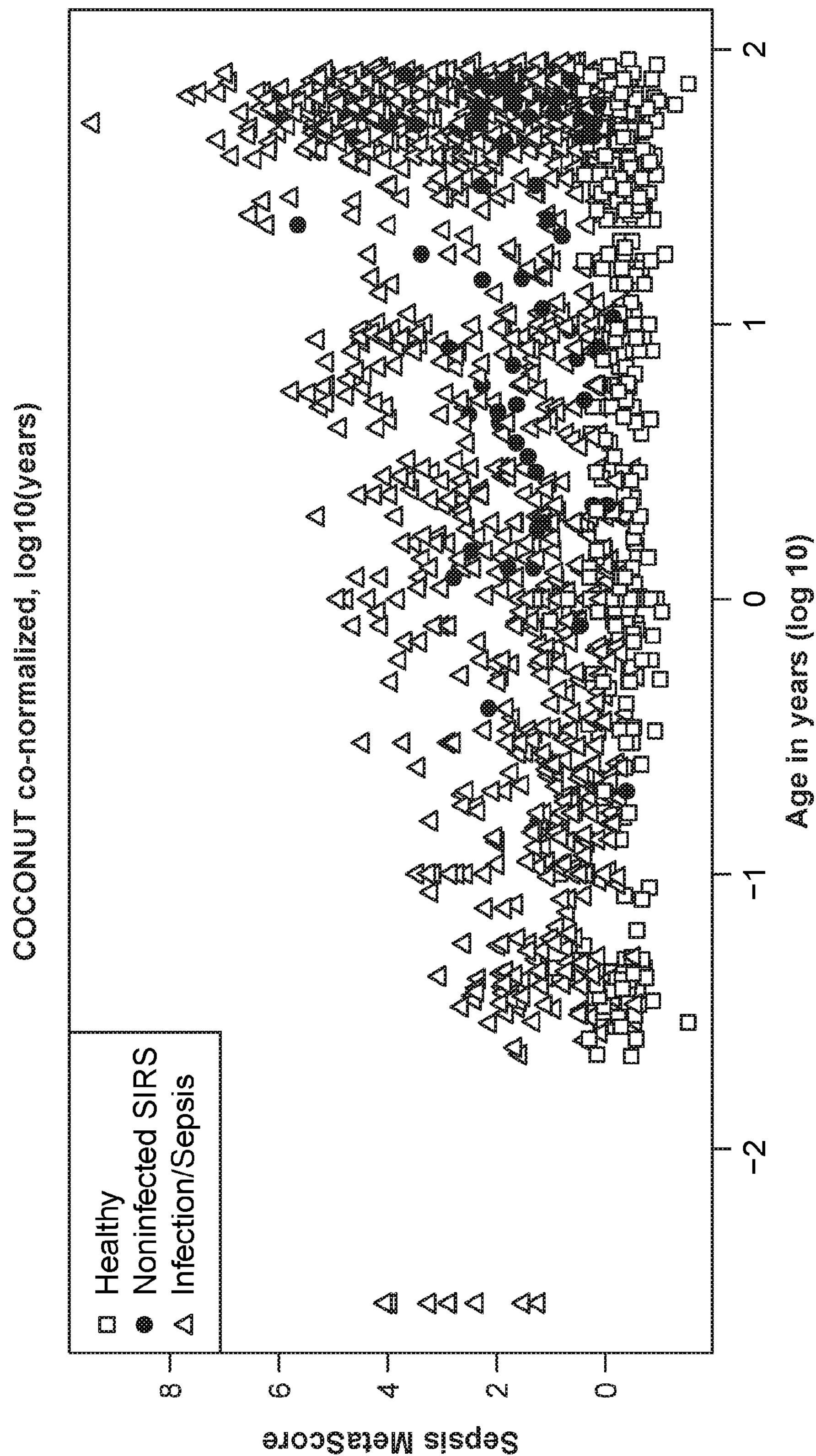


FIG. 19D

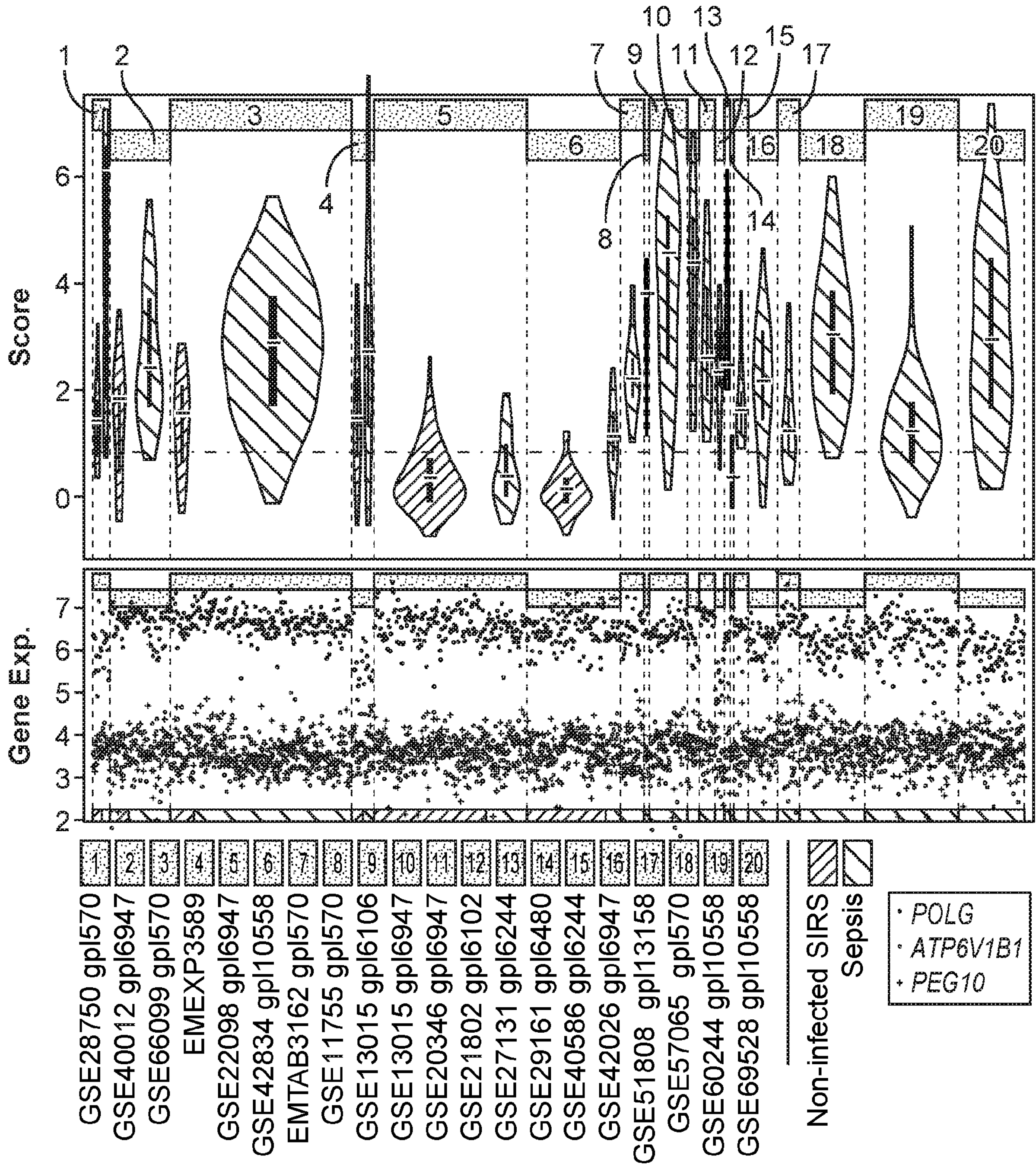


FIG. 20A

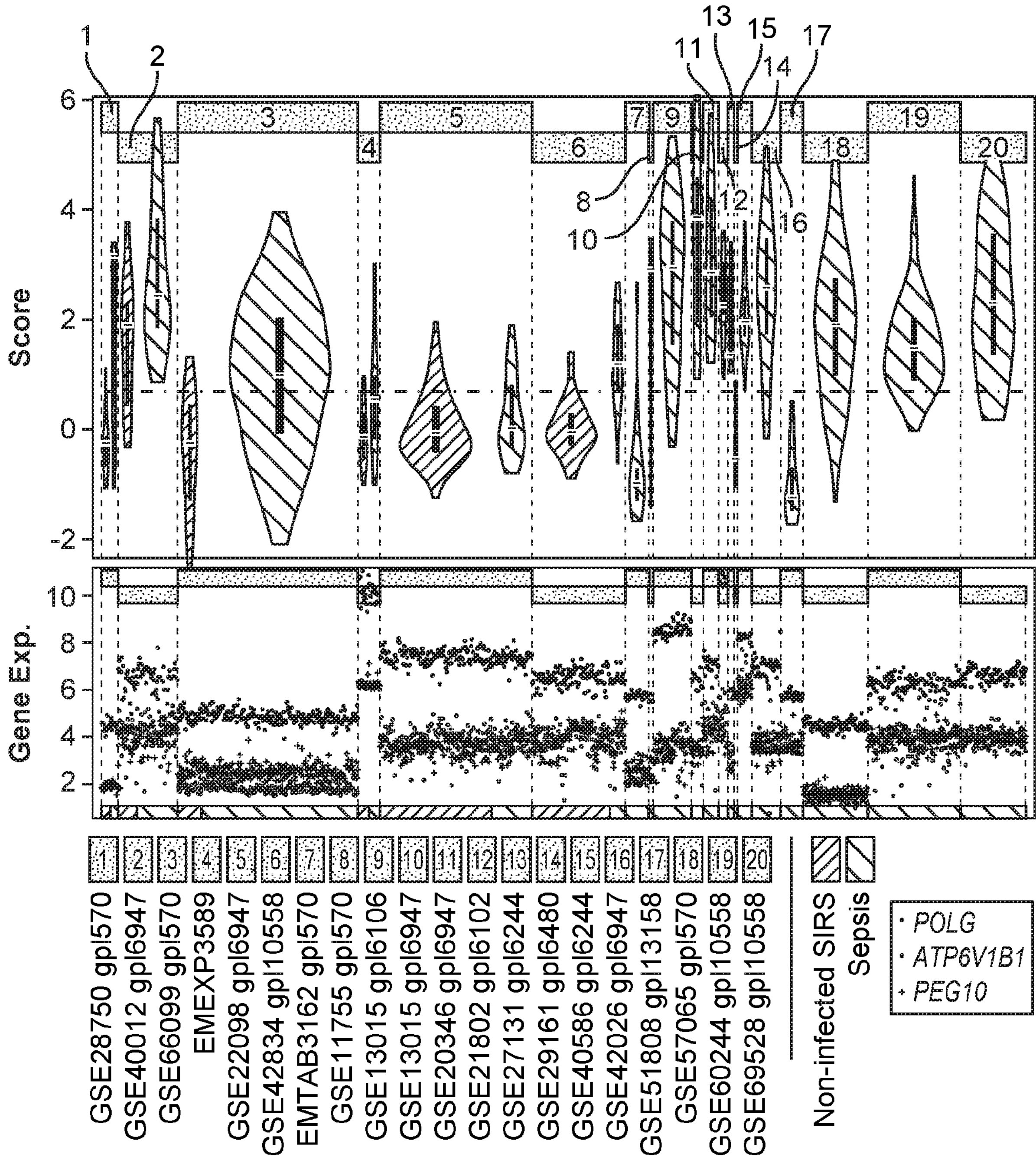


FIG. 20B

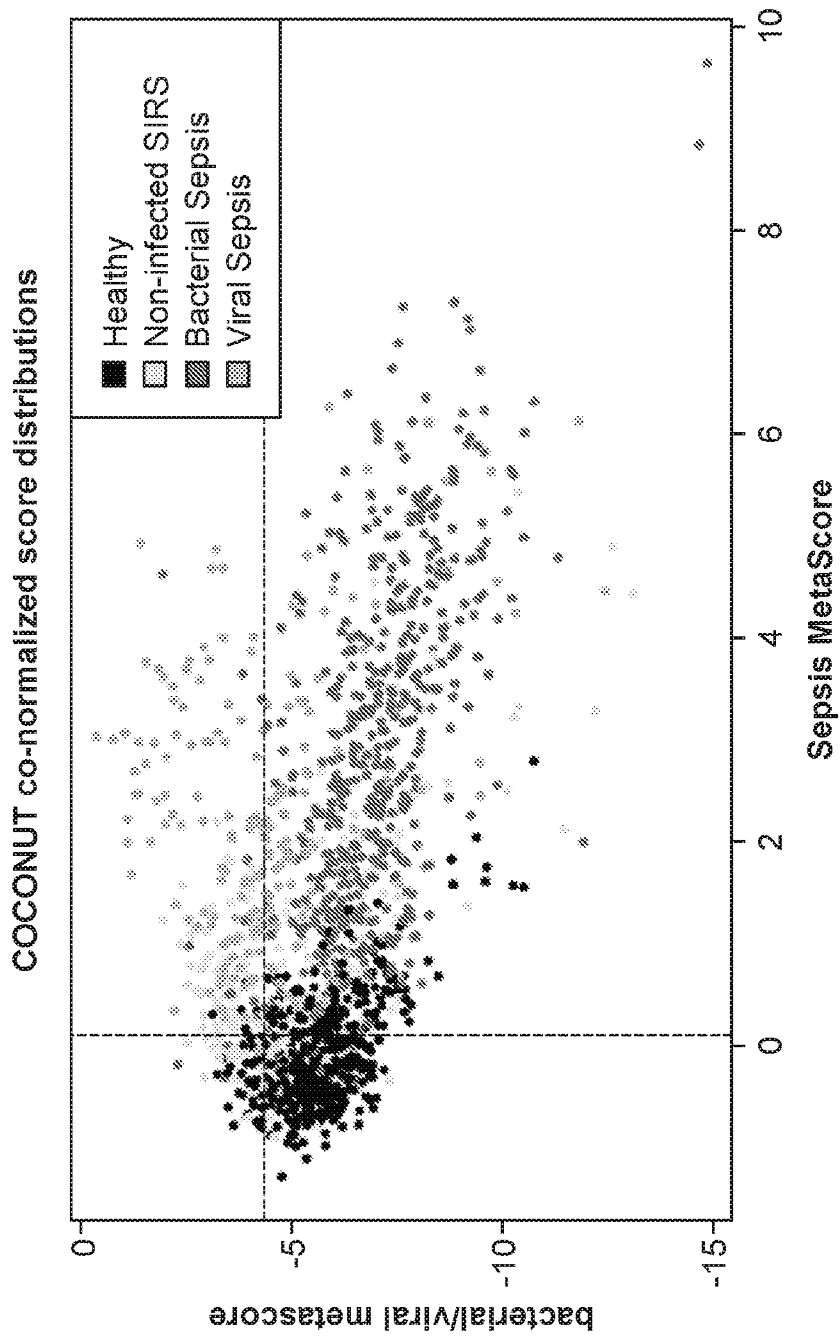


FIG. 21A

		Predicted		
		Healthy & SIRS	bacterial	viral
Ground Truth	Healthy & SIRS	560	245	72
	bacterial	19	505	12
	viral	1	94	107

FIG. 21B

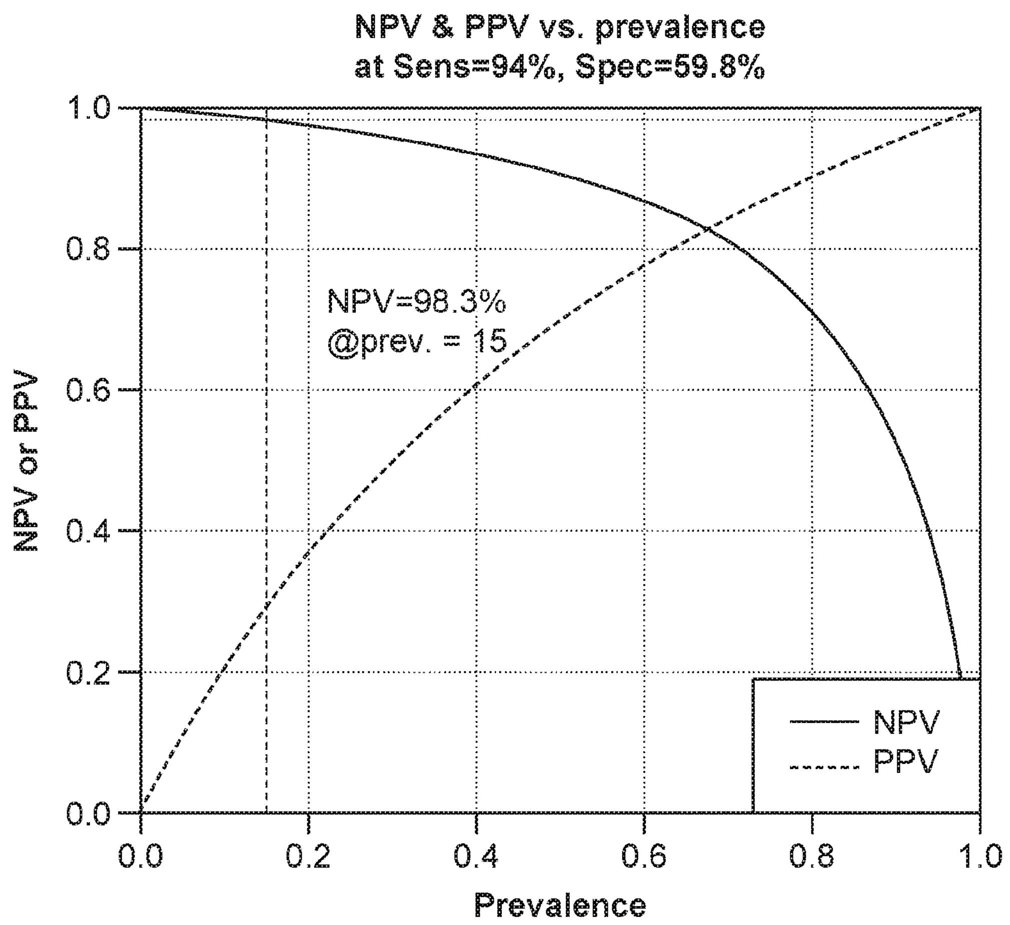


FIG. 22

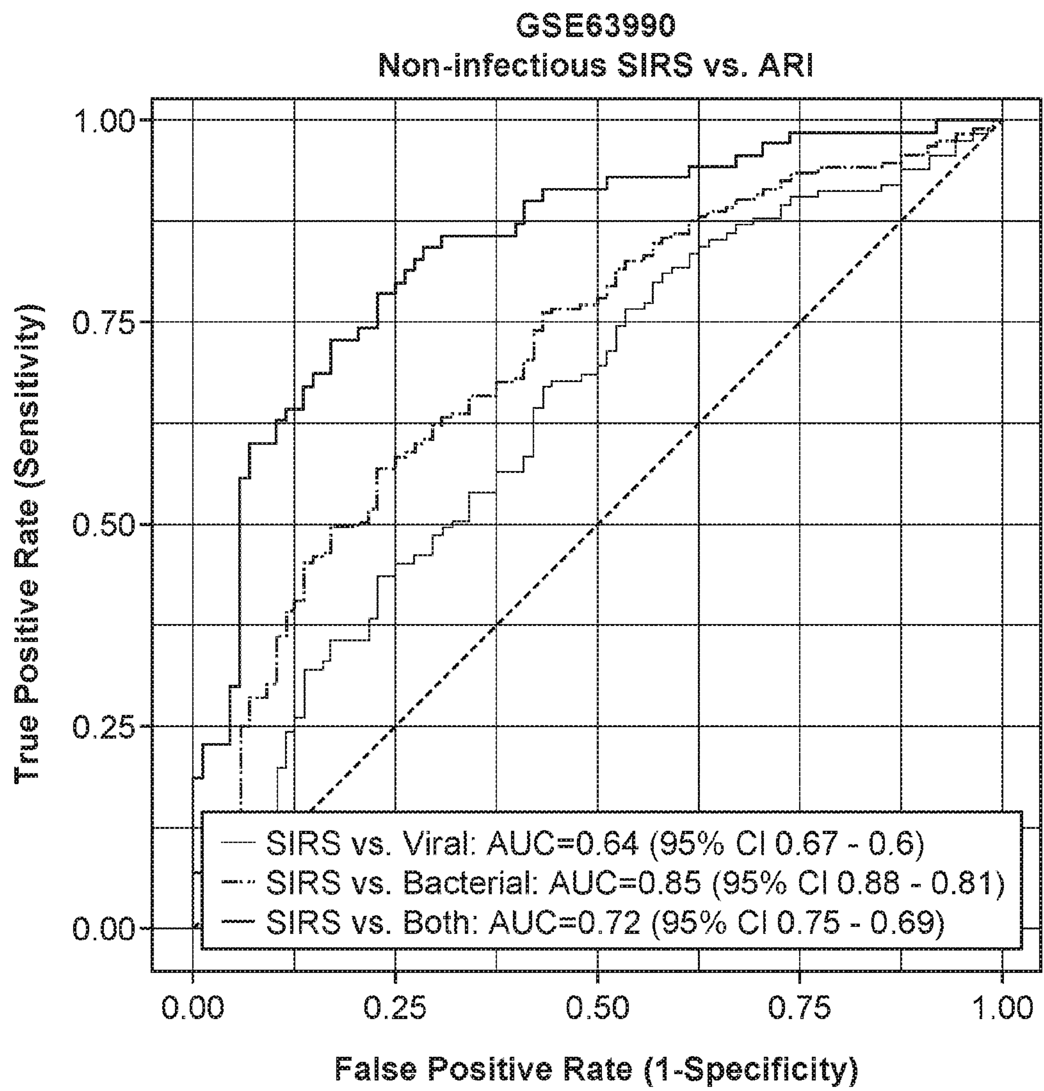


FIG. 23A

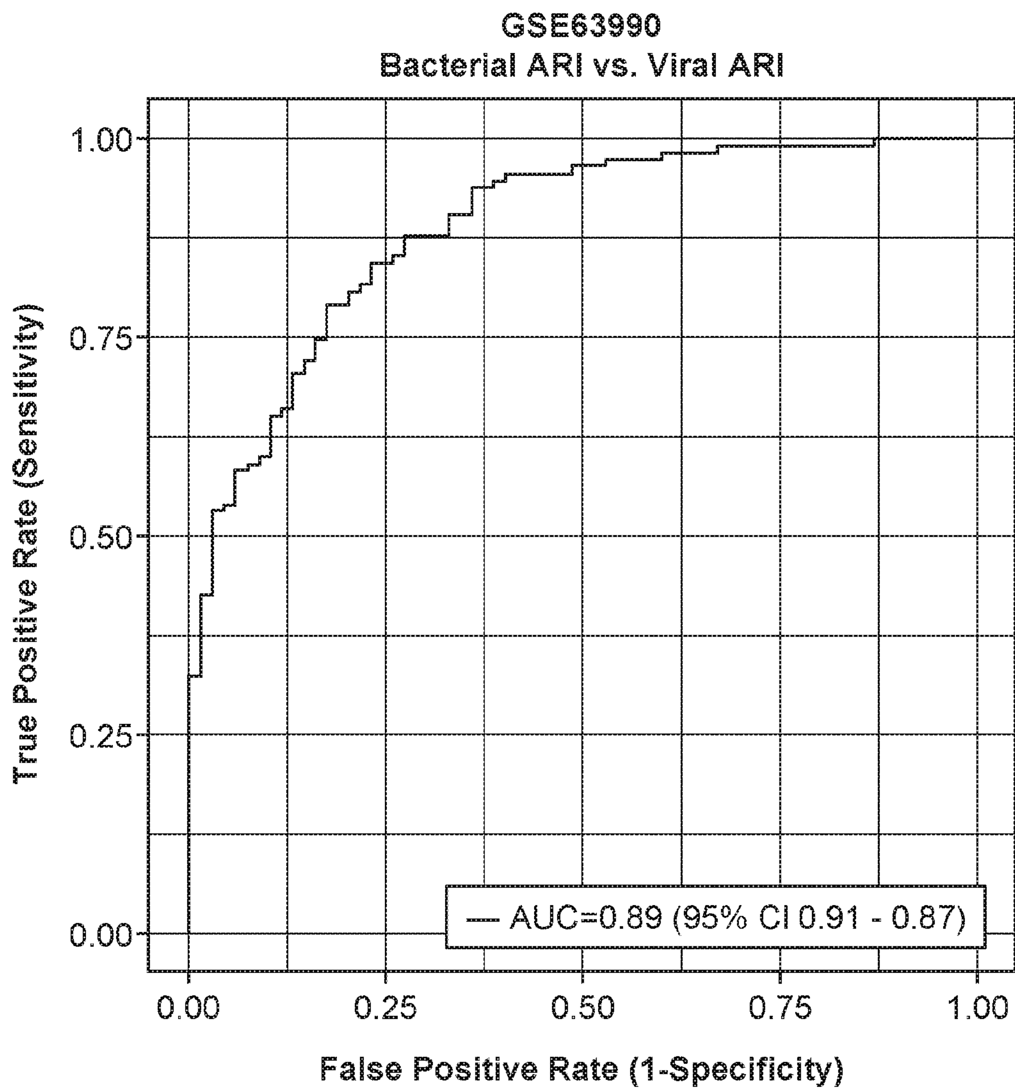


FIG. 23B

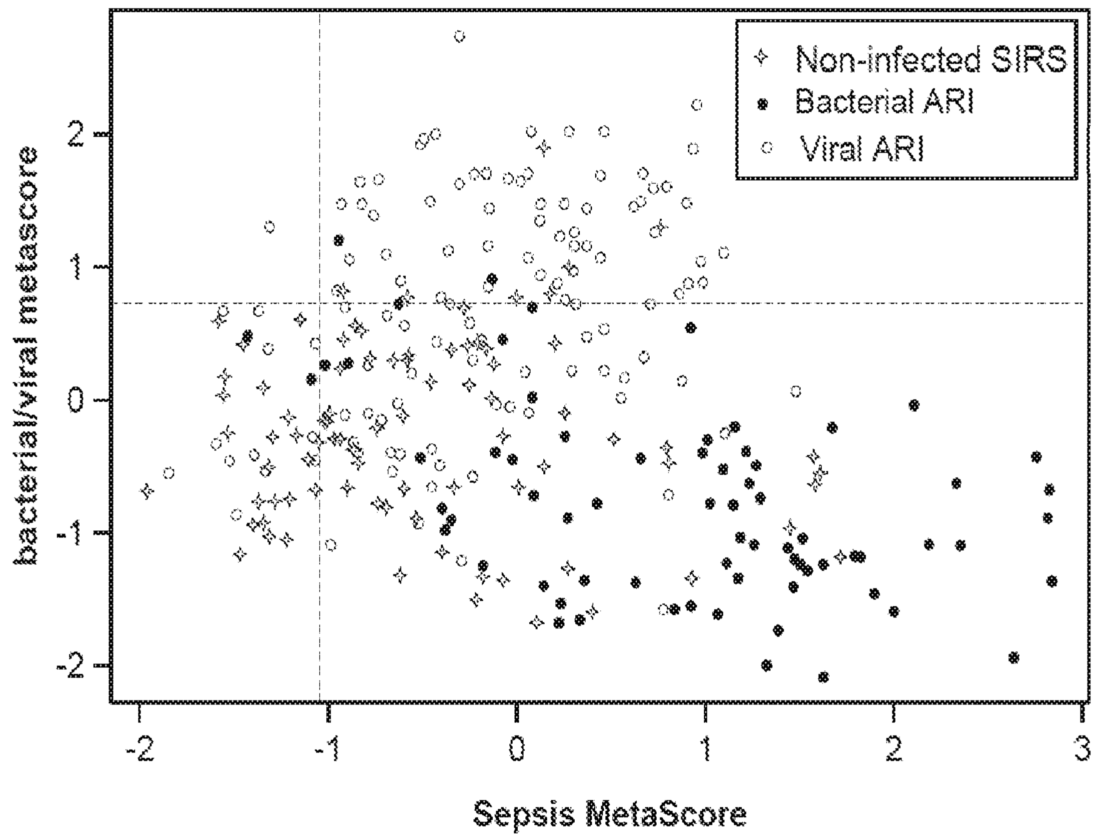


FIG. 23C

		Predicted		
		sterile SIRS	bact	viral
Ground Truth	sterile SIRS	25	56	7
	bact	2	66	2
	viral	14	41	60

FIG. 23D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/036003

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; G01N 33/53; G01N 33/569 (2017.01)
CPC - G01N 27/44726; G01N 33/56911; G01N 33/56983; G01N 2800/52 (2017.02)

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

B. FIELDS SEARCHED

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

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/5; 435/7.1; 436/501 (keyword delimited)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/0017630 A1 (MEMED DIAGNOSTICS LTD) 15 January 2015 (15.01.2015) entire document	1, 3, 18, 20, 24-27, 32, 34, 40, 41
A	US 2011/0275542 A1 (EDEN et al) 10 November 2011 (10.11.2011) entire document	1-3, 11-13, 18-22, 24-34, 38-41
A	US 2012/0053073 A1 (KASSIS) 01 March 2012 (01.03.2012) entire document	1-3, 11-13, 18-22, 24-34, 38-41
A	WO 2015/155517 A1 (THE UNIVERSITY COURT OF THE UNIVERSITY OF EDINBURGH) 15 October 2015 (15.10.2015) entire document	1-3, 11-13, 18-22, 24-34, 38-41
A	WO 2013/162651 A1 (US ARMY CENTER FOR ENVIRONMENTAL HEALTH RESEARCH (CEHR) et al) 31 October 2013 (31.10.2013) entire document	1-3, 11-13, 18-22, 24-34, 38-41

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2017	10 AUG 2017

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/036003

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

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

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

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

3. ☒ Claims Nos.: 4-10, 14-17, 23, 35-37
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:

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

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专利名称(译)	诊断细菌和病毒感染的方法		
公开(公告)号	EP3464645A1	公开(公告)日	2019-04-10
申请号	EP2017810802	申请日	2017-06-05
[标]申请(专利权)人(译)	斯坦福大学		
申请(专利权)人(译)	THE利兰·斯坦福，齐齐哈尔大学董事会		
当前申请(专利权)人(译)	THE利兰·斯坦福，齐齐哈尔大学董事会		
[标]发明人	KHATRI PURVESH SWEENEY TIMOTHY E		
发明人	KHATRI, PURVESH SWEENEY, TIMOTHY E.		
IPC分类号	C12Q1/68 G01N33/53 G01N33/569		
CPC分类号	C12Q1/6883 C12Q1/689 C12Q1/701 C12Q2600/158 G01N33/56911 G01N33/56983 G01N33/53 G01N33/569 G16B20/00 G16B25/10		
优先权	62/346962 2016-06-07 US		
其他公开文献	EP3464645A4		
外部链接	Espacenet		

摘要(译)

公开了诊断细菌和病毒感染的方法。特别地，本发明涉及可以确定患有急性炎症的患者是否患有细菌或病毒感染的生物标志物的用途。