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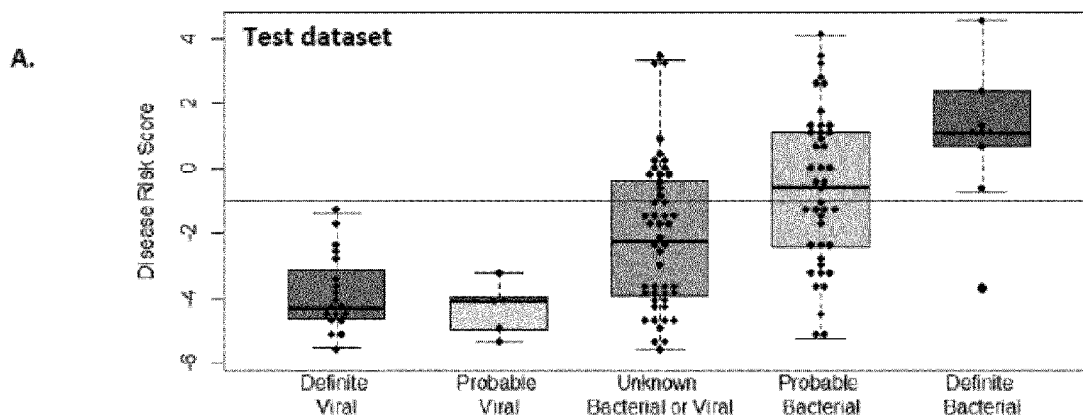
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(54) Title: METHOD OF IDENTIFYING A SUBJECT HAVING A BACTERIAL INFECTION

Figure 4



(57) Abstract: A method of identifying a subject having a bacterial infection, which includes discriminating said subject from a subject having a viral infection or an inflammatory disease. Also provided is a gene signature employed in the method and to a bespoke gene chip for use in the method. Further provided are probes and/or primers specific to genes in a signature of the present disclosure.

METHOD OF IDENTIFYING A SUBJECT HAVING A BACTERIAL INFECTION

The present disclosure relates to a method of identifying a subject having a bacterial infection, which includes discriminating said subject from a subject having a viral infection or an inflammatory disease. The disclosure also relates to a gene signature employed in the said method and to a bespoke gene chip for use in the method. The disclosure further extends to probes and/or primers specific to genes in a signature of the present disclosure. The disclosure further relates to use of known gene chips in the methods of the disclosure and kits comprising the elements required for performing the method. The disclosure also relates to use of the method to provide a composite expression score which can be used in the discrimination of a bacterial infection from a viral infection or inflammatory disease, particularly suitable for use in a low resource setting.

BACKGROUND

Every year, about 2.8 million children die in the first month of life, with 98% of these deaths occurring in developing countries. Neonatal infections, including sepsis and meningitis, are estimated to cause over 420 000 deaths each year, with 136 000 attributed to pneumonia. The current WHO recommendation for management of infections in neonates (0–28 days old) and young infants (0–59 days old) is referral for hospital treatment with at least a seven-day course of a combination of two injectable antibiotics – benzylpenicillin or ampicillin plus gentamicin. However, existing evidence demonstrates that in resource-limited settings many young infants with signs of severe infection do not receive the recommended inpatient treatment.

The vast majority of febrile children in the developed world have self-resolving viral infection, but a small proportion of them have life-threatening bacterial infections. Although microbiological culture of bacteria from normally sterile sites remains the “gold standard” for confirming bacterial infection, these bacterial culture tests have disadvantages. For instance, culture results may take several days, and are frequently falsely negative when the infection resides in inaccessible sites (such as the lung or abdominal cavity) or when antibiotics have been previously administered [1-3].

Current practice (for instance, UK NICE guidelines (<https://www.nice.org.uk/guidance/cg160>)) is to admit ill-appearing febrile children to hospital and to administer parenteral antibiotics while awaiting results from bacterial cultures [4-6]. However, as only a minority of febrile children are ultimately proven to have bacterial infection, many patients with febrile illness undergo unnecessary invasive investigation and antibiotic treatment when in fact they have self-resolving viral illness which does not require intervention. This therefore results in a major unnecessary burden on healthcare resources and inappropriate antibiotic prescription [7]. The latter is particularly problematic in the light of increasing antibiotic resistance found in bacteria. Hence, there is a need to avoid unnecessary administration of antibiotics.

Numerous attempts have been made to improve the identification of bacterial infection, such as serious bacterial infection (SBI), but the distinction between bacterial and viral infection remains problematic [44]. Clinical criteria, including symptoms, vital signs [45, 46], and blood markers such as white cell count, differential, C-reactive protein (CRP), or procalcitonin, do not reliably distinguish bacterial from viral infections [42, 46]. For example a study of 15,750 hospital attendances reported that only 7% had confirmed serious bacterial infection, and a further 7% had clinically diagnosed serious bacterial infection. However, of the remaining 13,500 children, 20% were still treated with

antibiotics. Conversely, 1% of those not suspected of having bacterial infection were re-admitted with serious bacterial infection, indicating that clinical diagnosis is very unreliable.¹⁰ Other studies have documented the high proportion of febrile children undergoing investigation and treatment with antibiotics, despite a low prevalence of confirmed SBI [5, 6].

In an attempt to improve pathogen identification in febrile children, various molecular tests have been proposed [8]. However blood culture tests and the results of pathogen detection by molecular approaches are often discordant [42], resulting in reduced confidence in the reliability of the molecular diagnostics. Rapid molecular viral diagnostic tests have increased the proportion of patients detected with respiratory pathogens [9], in particular viruses. However, the same viruses were also found frequently in nasopharyngeal samples from healthy children [10], limiting the clinical value of respiratory virus detection. Moreover, carrying viruses may predispose children to subsequently develop serious bacterial infection [43]. Thus, the detection of a virus in the nasopharynx of a febrile child does not rule out the possibility of a concurrent serious bacterial infection and is of little help in the decision on whether to administer or withhold antibiotics.

Thus there is a need for an improved method for identifying with confidence a subject with a bacterial infection in order to aid in the decision on whether to administer or withhold antibiotics from a subject.

SUMMARY OF THE INVENTION

The present inventors have generated data that suggests that a viable alternative to identifying specific pathogens in febrile children, is to employ the subjects inflammatory response to identify the presence of a bacterial infection. The present inventors' data indicates that induction of altered gene expression in host inflammatory cells is likely to be a marker for specific childhood infections including tuberculosis [11], bacterial [47, 12], including in the presence of viral infections [13-15, 48].

The present disclosure is summarised in the following paragraphs:

1. A method for identifying a subject having a bacterial infection comprising detecting in a subject derived RNA sample the modulation in gene expression levels of a gene signature comprising two or more genes, but no more than 10 genes, selected from the group consisting of: *IFI44L*, *FAM89A*, *IFI27L*, *IFT11*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
2. The method according to paragraph 1, wherein the gene signature comprises two or more genes but no more than 10 genes selected from the group consisting of: *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *ESPTI1*, *OAS1*, *IFI6*, *HS.386275*, *EIF2AK2*, *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
3. The method according to paragraph 1 or 2, wherein the gene signature comprises at least one gene selected from the group consisting of:
 - a) *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *OAS1*, *IFI6*, *HS.386275*, *EIF2AK2*; and optionally one or more genes selected from the group consisting of:
 - b) *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
4. The method according to claim 3, wherein the gene signature comprises at least one gene from each of the following groups:

- a) *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *OAS1*, *IFI6*, *HS.386275* and *EIF2AK2*; and
 - b) *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
5. A method according to any one of the preceding paragraphs, wherein the gene signature is based on two genes of primary importance.
 6. A method according to any one of the preceding paragraphs, wherein the gene signature comprises one or more of the following pairs of genes: *IFI44L* and *FAM89A*, *OAS1* and *EMR1*, *EMR1* and *IFI44L*, *OAS1* and *FAM89A*, *EBI3* and *IFI44L*, *S100P* and *RSAD2*, *SLPI* and *IFI44L*, *S100P* and *EPSTI1*, *S100P* and *IFI44L*, *OAS1* and *FAM89A*, *EMR1* and *RSAD2*, *IFIT3* and *FAM89A*, *TMEM119* and *IFI44L*, *IFIT3* and *EMR1*, *IFI6* and *FAM89A*, *EPSTI1* and *FAM89A*, *IFIT3* and *FAM89A*, *UPB1* and *IFI44L*, *S100P* and *IFIT1*, *RSAD2* and *FAM89A*, *EMR1* and *EPSTI1*, *S100P* and *EIF2AK2*, *IFIT3* and *FAM89A*, *OAS1* and *SLPI*, *IFIT1* and *FAM89A*, *IFIT3* and *SLPI*, *EMR1* and *IFIT3*, *OAS1* and *S100P*, *IFIT1* and *SLPI*, *IFIT1* and *EMR1*, *FAM89A* and *EPSTI1*, *SLPI* and *RSAD2*, *S100P* and *IFIT2*, *IFIT1* and *TMEM119*, *IFIT1* and *FAM89A*, *SLPI* and *EPSTI1*, *FAM89A* and *IFIT3*, *OAS1* and *EBI3*, *EIF2AK2* and *FAM89A*, *EBI3* and *EPSTI1*, *IFIT3* and *S100P*, *S100P* and *IFI6*, *OTOF* and *S100P*, *OAS1* and *TMEM119*, *EBI3* and *RSAD2*, *OTOF* and *EBI3*, *S100P* and *IFIT3*, *OTOF* and *FAM89A*, *IFIT2* and *FAM89A*, *IFI27* and *FAM89A*, *OAS1* and *UPB1*, *OTOF* and *FAM89A*, *IFIT1* and *UPB1*, *EIF2AK2* and *FAM89A*, *RSAD2* and *UPB1*, *IFIT3* and *EBI3*, *SLPI* and *IFIT2*, *SLPI* and *IFIT3*, *EMR1* and *IFIT2*, *HS.386275* and *EBI3*, *HS.386275* and *UPB1*, *IFIT3* and *UPB1*, *HS.386275* and *UPB1*, *IFIT3* and *UPB1*, *HS.386275* and *SLPI*, *FAM89A* and *IFI6*, *SLPI* and *IFI27*, *PTPN20* and *IFI44L*, *OTOF* and *UPB1*, *HS.386275* and *S100P*, *S100P* and *IFI27*, *EIF2AK2* and *UPB1*, *EBI3* and *IFI27*, *IFI44L* and *KCNMA1*, *TMEM119* and *EPSTI1*, *IFIT2* and *TMEM119*, *SLPI* and *IFI6*, *IFIT3* and *TMEM119*, *UPB1* and *EPSTI1*, *IFIT1* and *EBI3*, *RSAD2* and *PTPN20*, *EBI3* and *IFIT3*, *IFI44L* and *MERTK*, *EBI3* and *IFI6*, *PI3* and *IFI27*, *IFI2* and *UPB1*, *HS.386275* and *TMEM119*, *IFIT2* and *EBI3*, *TMEM119* and *IFIT3*, *IFIT2* and *MERTK*, *EIF2AK2* and *EBI3*, *S100P* and *SERPING1*, *RSAD2* and *MERTK*, *IFIT3* and *MERTK*, *UPB1* and *IFIT3*, *SERPING1* and *FAM89A*, *IFIT3* and *PTPN20*, *KCNMA1* and *EPSTI1*, *IFIT3* and *KCNMA1*, *SERPING1* and *FAM89A*, *OAS1* and *PTPN20*, *PTPN20* and *EPSTI1*, *OTOF* and *KCNMA*, and *PTPN20* and *IFIT3*.
 7. The method according to any one of the preceding paragraphs, wherein the gene signature comprises at least *IFI44L* and *FAM89A*.
 8. The method according to any one of the preceding paragraphs, wherein the gene signature comprises at least *OAS1* and *EMR1*.
 9. The method according to any one of the preceding paragraphs, wherein the gene signature comprises at least *IFI44L* and *IFI27*.
 10. The method according to any one of paragraphs 1 to 6, wherein the gene signature consists of *IFI44L* and *FAM89A*.
 11. The method according to any one of paragraphs 1 to 6, wherein the gene signature consists of *OAS1* and *EMR1*.
 12. The method according to any one of paragraphs 1 to 6, wherein the gene signature consists of *IFI44L* and *IFI27*.
 13. The method according to any one of the preceding paragraphs, wherein the gene expression levels of one or more of the genes selected from the group consisting of *FAM89A*, *KCNMA1*,

MERTK, EBI3, UPB1, EMR1, PTPN20, TMEM119, SLPI, S100P and *PI3* are upregulated in a subject having a bacterial infection.

14. The method according to any one of the preceding paragraphs, wherein the gene expression levels of one or more of the genes selected from the group consisting of *IFI44L, IFI27, IFIT1, RSAD2, IFIT3, OTOF, IFIT2, EPSTI1, SERPING1, OAS1, IFI6, HLA-DRB6, HBZ, HS.386275, EIF2AK2, IFIT1L, FCER1A, C21ORF7, GYPE, GYPB, HBM, EIF1AY, LOC649143, HBD* and *FBXO7* and are downregulated in a subject having a bacterial infection.
15. A method according to any one of the preceding paragraphs, wherein the gene signature employs no more than a total of 10 genes, for example no more than 5 genes, such as 2, 3, 4, or 5 genes.
16. The method according to any one of the preceding paragraphs, wherein the method incorporates one or more such as 1, 2, 3, 4 or 5 housekeeping genes.
17. The method according to any one of the preceding paragraphs, wherein the method is for discriminating a subject having a bacterial infection from a subject having a viral infection.
18. The method according to any one of the preceding claims, wherein the method is for discriminating a subject having a bacterial infection from a subject having an inflammatory disease.
19. The method according to any one of the preceding paragraphs, wherein the bacterial infection is selected from the group consisting of: *Chlamydia pneumoniae, Chlamydia trachomatis, Chlamydophila psittaci, Mycoplasma pneumonia, Corynebacterium diphtheriae, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Clostridium tetani, Enterococcus faecalis, Enterococcus faecium, Listeria monocytogenes, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Group B streptococcus, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes*, or acid fast bacteria such as *Mycobacterium leprae, Mycobacterium tuberculosis, Mycobacterium ulcerans, mycobacterium avium intercellularae, Bordetella pertussis, Borrelia burgdorferi, Brucella abortus, Brucella canis, Brucella melitensis, Brucella suis, Campylobacter jejuni, Escherichia coli, Francisella tularensis, Haemophilus influenzae, Helicobacter pylori, Legionella pneumophila, Leptospira interrogans, Neisseria gonorrhoeae, Neisseria meningitidis, Pseudomonas aeruginosa, Pseudomonas spp, Rickettsia rickettsii, Salmonella typhi, Salmonella typhimurium, Shigella sonnei, Treponema pallidum, Vibrio cholerae, Yersinia pestis, Kingella kingae, Stenotrophomonas* and *Klebsiella*.
20. The method according to any one of claims the preceding paragraphs, wherein the bacterial infection is a serious bacterial infection, for example bacterial meningitis, a respiratory infection, a urinary tract infection and/or bacteraemia.
21. The method according to any one of the preceding paragraphs, wherein a subject with bacterial infection can be identified in the presence of viral infection and/or an inflammatory disease.
22. The method according to any one of paragraphs 1 to 20, wherein a subject with bacterial infection can be discriminated from a patient with viral infection and/or inflammatory disease only.
23. The method according to any one of the preceding paragraphs, wherein the viral infection is selected from the group consisting of: Influenza such as Influenza A, including but not limited to: H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, Influenza B and Influenza C, Respiratory Syncytial Virus (RSV), rhinovirus, enterovirus, bocavirus, parainfluenza, adenovirus, metapneumovirus, herpes simplex virus, Chickenpox virus, Human papillomavirus,

Hepatitis, Epstein-Barr virus, Varicella-zoster virus, Human cytomegalovirus, Human herpesvirus, type 8 BK virus, JC virus, Smallpox, Parvovirus B19, Human astrovirus, Norwalk virus, coxsackievirus, poliovirus, Severe acute respiratory syndrome virus, yellow fever virus, dengue virus. West Nile virus. Rubella virus. Human immunodeficiency virus, Guanarito virus, Junin virus, Lassa virus, Machupo virus, Sabia virus, Crimean-Congo haemorrhagic fever virus, Ebola virus, Marburg virus, Measles virus, Mumps virus, Rabies virus and Rotavirus.

24. The method according to any one of the preceding claims, wherein the inflammatory disease is juvenile idiopathic arthritis (JIA), Henoch-Schönlein purpura (HSP) or systemic lupus erythematosus (SLE).
25. The method according to any one of the preceding paragraphs, wherein the subject is a child.
26. The method according to claim 25, where the child is in the age range 2 to 59 months.
27. The method according to any one of paragraphs 1 to 24, wherein the subject is an infant in the age range 0 to 59 days.
28. The method according to any one of the preceding paragraphs, wherein the subject has a fever.
29. The method according to any one of the preceding paragraphs, wherein a patient derived sample is employed in the method.
30. The method according to any one of the preceding paragraphs wherein the analysis of gene expression modulation employs a microarray.
31. The method according to any one of paragraphs 1 to 29, wherein the analysis gene expression modulation employs PCR, such as RT-PCR.
32. The method according to paragraph 31, wherein the PCR is a multiplex PCR.
33. The method according to claim 31 or 32, wherein the PCR is quantitative.
34. The method according to any one of claims 31 to 33, wherein primers employed in the PCR comprise a label or a combination of labels.
35. The method according to paragraph 34, wherein the label is fluorescent or coloured, for example coloured beads.
36. The method according to any one of paragraphs 31 to 35, wherein the analysis of gene expression modulation employs a dual colour reverse transcriptase multiplex ligation dependent probe amplification.
37. The method according to any one of the preceding paragraphs wherein gene expression modulation is detected by employing fluorescence spectroscopy.
38. The method according to any one of paragraphs 1 to 36, wherein gene expression modulation is detected by employing colourimetric analysis.
39. The method according to any one of paragraphs 1 to 36, wherein gene expression modulation is detected by employing impedance spectroscopy.
40. The method according to any one of the preceding paragraphs, which comprises the further step of prescribing a treatment for the subject based on the results of the analysis of said gene signature.
41. A method of treating a patient by administering an anti-bacterial agent such as an antibiotic, wherein the patient is characterised in that they have been identified as positive for bacterial infection by the method defined in any one of paragraphs 1 to 39.

42. A method of treating a patient by administering an anti-viral agent, such as oseltamivir or peramivir, wherein the patient is characterised in that they have been identified as negative for bacterial infection by the defined in any one of paragraphs 1 to 39.
43. A set of primers for use in multiplex PCR wherein the set of primers includes nucleic acid sequences specific to a polynucleotide gene transcript for at least one gene from the group consisting of:
 - a) *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *OAS1*, *IFI6*, *HS.386275* and *EIF2AK2*; and optionally includes nucleic acid sequences specific to a polynucleotide gene transcript for one or more genes selected from the group consisting of:
 - b) *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
44. The set of primers according to paragraph 43 wherein the set of primers includes nucleic acid sequences specific to a polynucleotide gene transcript for at least one gene from each of the following groups:
 - a) *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *OAS1*, *IFI6*, *HS.386275*, *EIF2AK2*; and
 - b) *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
45. The set of primers according to paragraphs 43 or 44, wherein the nucleic acid sequences in the set are for no more than a total of 5 genes, such as 2, 3, 4, or 5 genes.
46. The set of primers according to any one of claims 43 to 45, wherein gene transcript is RNA, for example mRNA.
47. The set of primers according to any one of paragraphs 43 to 46 wherein the set of primers includes one or more nucleic acids sequences specific to a gene transcript encoding *IFI44L*, for example the *IFI44L* sequence shown in SEQ ID NO: 1
48. The set of primers according to any one of paragraphs 43 to 47, wherein the set of primers includes one or more nucleic acid sequences specific to a gene transcript encoding *FAM89A*, for example the *FAM89A* sequence shown in SEQ ID NO: 2.
49. The set of primers according to any one of paragraphs 43 to 48, wherein the primers for each gene are at least a pair of nucleic acid primer sequences.
50. The set of primers according to any one of paragraphs 43 to 48 wherein the primer length is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100 bases in length.
51. The set of primers according to any one of paragraphs 43 to 50, wherein at least one primer for each gene comprises a label.
52. The set of priers according to paragraph 51, wherein the labels on the primers are independently selected from selected from a fluorescent label, a coloured label, and antibody, step tag, his tag.
53. The set of primers according to paragraph 51 or 52, where each primer in a given pair of primers is labelled, for example where one label quenches the fluorescence of the other label when said labels are within proximity of each other.
54. The set of primers according to any one of paragraphs 43 to 53, wherein the primers comprise or consist of the sequences given in any one of SEQ ID NOs: 3 to 40.

55. A point of care test for identifying bacterial infection in a subject comprising the set of primers defined in any one of paragraphs 43 to 54.

56. Use of the set of primers defined in any one of paragraphs 43 to 54 in an assay to detect bacterial infection in a sample, for example a blood sample.

Accordingly, the present disclosure also provides a method for discriminating a subject having a bacterial infection from a subject having a viral infection or an inflammatory disease, comprising detecting in a subject derived RNA sample the modulation in gene expression levels of a gene signature comprising 2 or more genes selected from the group consisting of: *IFI44L*, *FAM89A*, *IFI27L*,
5 *IFT11*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In one embodiment, the gene expression levels of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18,
10 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35 or 36 of the genes listed above are detected.

In one embodiment, the gene expression levels of all 36 genes listed above are detected. Accordingly, in one embodiment there is provided a method for identifying a subject having a bacterial infection comprising detecting in a subject derived RNA sample the modulation in gene expression levels of a gene signature consisting of the following genes: *IFI44L*, *FAM89A*, *IFI27L*, *IFT11*, *RSAD2*, *IFIT3*, *OTOF*,
15 *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

Advantageously, use of the appropriate gene signature in a method according to the present disclosure allows the robust and accurate identification of the presence of a bacterial infection or the
20 differentiation of a bacterial infection from a viral infection or an inflammatory disease. Importantly, the method allows the accurate discrimination between bacterial and viral infections in patients displaying symptoms of bacterial and/or viral infections. In other words, the method allows the accurate detection of a bacterial infection in the presence or absence of a viral infection, without the need to rely on clinical criteria and/or bacterial culture tests.

25 What is more the gene signature of the present disclosure is based on as little as two genes.

Gene signatures often comprise a large number of genes which only in combination show a pattern or marker of biological significance. It is very surprising that the gene signature of the present disclosure can be based on as little as a two genes and still reliably identify the presence of a bacterial infection.

30 The identification of bacterial infection can be particularly critical in patients which display clinical symptoms of having a viral infection only but in reality also have an underlying acute bacterial infection, such as a serious bacterial infection.

There is a significant unmet clinical need for proper and reliable identification of bacterial infection, particularly in children and infants. The gene signature of the present disclosure is a huge step
35 forward on the road to treating patients, such as febrile patients because it allows accurate and rapid diagnosis which, in turn, allows patients to be appropriately and timely treated.

Furthermore, the components employed in the method disclosed herein can be provided in a simple format, which are cost efficient, rapid, cost effective, and can be employed in low resource and/or rural settings.

In one embodiment of the disclosure, the gene signature comprises at least one gene from each of the following groups:

- a) *IFI44L, IFI27, IFIT1, RSAD2, IFIT3, OTOF, IFIT2, EPSTI1, SERPING1, OAS1, IFI6, HLA-DRB6, HBZ, HS.386275, EIF2AK2, IFIT1L, FCER1A, C21ORF7, GYPE, GYPB, HBM, EIF1AY, LOC649143, HBD* and *FBXO7*; and
- b) *FAM89A, KCNMA1, MERTK, EBI3, UPB1, EMR1, PTPN20, TMEM119, SLPI, S100P* and *PI3*.

In one embodiment, the gene signature comprises at least one gene selected from the group consisting of:

- a) *IFI44L, IFI27, IFIT1, RSAD2, IFIT3, OTOF, IFIT2, EPSTI1, OAS1, IFI6, HS.386275, EIF2AK2*; and optionally one or more genes selected from the group consisting of:
- b) *FAM89A, KCNMA1, MERTK, EBI3, UPB1, EMR1, PTPN20, TMEM119, SLPI, S100P* and *PI3*.

In one embodiment of the disclosure, the gene signature comprises at least one gene from each of the following groups:

- a) *IFI44L, IFI27, IFIT1, RSAD2, IFIT3, OTOF, IFIT2, EPSTI1, OAS1, IFI6, HS.386275* and *EIF2AK2*; and
- b) *FAM89A, KCNMA1, MERTK, EBI3, UPB1, EMR1, PTPN20, TMEM119, SLPI, S100P* and *PI3*.

The present inventors found that the genes in group a) tend to be down-regulated in subjects having a bacterial infection, whilst the genes in group b) tend to be up-regulated in subjects having a bacterial infection. Surprisingly, the present inventors have discovered that having at least one gene from each group in the gene signature provides sufficiently discriminatory power to identify subjects having a bacterial infection including discriminating subjects having a bacterial infection from a viral infection or inflammatory disease. Furthermore, the method is also suitable for identify bacterial infection in the presence of a viral infection or inflammatory disease.

In one embodiment, the gene signature comprises or consists of one or more of the following pairs of genes: *IFI44L* and *FAM89A*, *OAS1* and *EMR1*, *EMR1* and *IFI44L*, *OAS1* and *FAM89A*, *EBI3* and *IFI44L*, *S100P* and *RSAD2*, *SLPI* and *IFI44L*, *S100P* and *EPSTI1*, *S100P* and *IFI44L*, *OAS1* and *FAM89A*, *EMR1* and *RSAD2*, *IFIT3* and *FAM89A*, *TMEM119* and *IFI44L*, *IFIT3* and *EMR1*, *IFI6* and *FAM89A*, *EPSTI1* and *FAM89A*, *IFIT3* and *FAM89A*, *UPB1* and *IFI44L*, *S100P* and *IFIT1*, *RSAD2* and *FAM89A*, *EMR1* and *EPSTI1*, *S100P* and *EIF2AK2*, *IFIT3* and *FAM89A*, *OAS1* and *SLPI*, *IFIT1* and *FAM89A*, *IFIT3* and *SLPI*, *EMR1* and *IFIT3*, *OAS1* and *S100P*, *IFIT1* and *SLPI*, *IFIT1* and *EMR1*, *FAM89A* and *EPSTI1*, *SLPI* and *RSAD2*, *S100P* and *IFIT2*, *IFIT1* and *TMEM119*, *IFIT1* and *FAM89A*, *SLPI* and *EPSTI1*, *FAM89A* and *IFIT3*, *OAS1* and *EBI3*, *EIF2AK2* and *FAM89A*, *EBI3* and *EPSTI1*, *IFIT3* and *S100P*, *S100P* and *IFI6*, *OTOF* and *S100P*, *OAS1* and *TMEM119*, *EBI3* and *RSAD2*, *OTOF* and *EBI3*, *S100P* and *IFIT3*, *OTOF* and *FAM89A*, *IFIT2* and *FAM89A*, *IFI27* and *FAM89A*, *OAS1* and *UPB1*, *OTOF* and *FAM89A*, *IFIT1* and *UPB1*, *EIF2AK2* and *FAM89A*, *RSAD2* and *UPB1*, *IFIT3* and *EBI3*, *SLPI* and *IFIT2*, *SLPI* and *IFIT3*, *EMR1* and *IFIT2*, *HS.386275* and *EBI3*, *HS.386275* and *UPB1*, *IFIT3* and *UPB1*, *HS.386275* and *UPB1*, *IFIT3* and *UPB1*, *HS.386275* and *SLPI*, *FAM89A* and *IFI6*, *SLPI* and *IFI27*, *PTPN20* and *IFI44L*, *OTOF* and *UPB1*, *HS.386275* and *S100P*, *S100P* and *IFI27*, *EIF2AK2* and *UPB1*, *EBI3* and *IFI27*, *IFI44L* and *KCNMA1*, *TMEM119* and *EPSTI1*, *IFIT2* and *TMEM119*, *SLPI* and *IFI6*, *IFIT3* and *TMEM119*, *UPB1* and *EPSTI1*,

IFIT1 and *EBI3*, *RSAD2* and *PTPN20*, *EBI3* and *IFIT3*, *IFI44L* and *MERTK*, *EBI3* and *IFI6*, *PI3* and *IFI27*, *IFI2* and *UPB1*, *HS.386275* and *TMEM119*, *IFIT2* and *EBI3*, *TMEM119* and *IFIT3*, *IFIT2* and *MERTK*, *EIF2AK2* and *EBI3*, *S100P* and *SERPING1*, *RSAD2* and *MERTK*, *IFIT3* and *MERTK*, *UPB1* and *IFIT3*, *SERPING1* and *FAM89A*, *IFIT3* and *PTPN20*, *KCNMA1* and *EPSTI1*, *IFIT3* and *KCNMA1*, *SERPING1* and *FAM89A*, *OAS1* and *PTPN20*, *PTPN20* and *EPSTI1*, *OTOF* and *KCNMA*, and *PTPN20* and *IFIT3*.

In one embodiment, the gene signature comprises or consists of one or more of the following pairs of genes: *IFI44L* and *IFI27*, *IFIT1* and *IFI27*, *RSAD2* and *IFI27*, *IFIT2* and *IFI27*, *IFIT3* and *IFI27*, *IFI27* and *EPSTI1*, *S100P* and *EBI3*, and *EIF2AK2* and *IFI27*.

In one embodiment, the gene expression levels of one or more of the genes selected from the group consisting of *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3* are upregulated in a subject having a bacterial infection.

In one embodiment, the gene expression levels of one or more of the genes selected from the group consisting of *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD* and *FBXO7* are downregulated in a subject having a bacterial infection.

In another embodiment of the disclosure, the gene signature comprises at least 95%, such as 100% of the genes *IFI44L*, *FAM89A*, *IFI27L*, *IFTI1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In one embodiment of the disclosure, the gene signature comprises *IFI44L* and *FAM89A*. In another embodiment, the gene signature comprises *OAS1* and *EMR1*. In yet another embodiment, the gene signature comprises *IFI44L* and *IFI27*.

In addition to any of the pair of genes listed above, the gene signature may further comprise one or more of the following genes: *IFI27L*, *IFTI1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In another embodiment, the gene signature may further comprise one or more of the following genes: *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *ESPTI1*, *OAS1*, *IFI6*, *HS.386275*, *EIF2AK2*, *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In one embodiment of the disclosure, the gene signature comprises *IFI44L* and *FAM89A* and at least one further gene selected from:

- a) *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD* and *FBXO7*; and at least a further gene selected from:
- b) *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*, for example where the gene signature comprises between 2 and 10 genes, such as 3, 4, 5, 6, 7, 8 or 9 genes.

In one embodiment of the disclosure, the gene signature comprises *OAS1* and *EMR1* and at least one further gene selected from:

- a) *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD* and *FBXO7*; and at least a further gene selected from:
- b) *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*, for example where the gene signature comprises between 2 and 10 genes, such as 3, 4, 5, 6, 7, 8 or 9 genes.

In one embodiment of the disclosure, the gene signature comprises *IFI44L* and *IFI27* and at least one further gene selected from:

- a) *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD* and *FBXO7*; and at least a further gene selected from:
- b) *FAM89A*, *KCNMA1*, *MERTK*, *EMR1*, *EBI3*, *UPB1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*, for example where the gene signature comprises between 2 and 10 genes, such as 3, 4, 5, 6, 7, 8 or 9 genes.

Advantageously, the present inventors were able to discriminate subjects having a bacterial infection from subjects having a viral infection with a high degree of sensitivity (100%) and specificity (above 85%) using a gene signature which detects the modulation in gene expression levels of the 36 genes listed above.

In one embodiment the gene signature of the present disclosure employs no more than 5 genes.

In one embodiment the gene signature is based on 2 genes of primary importance.

In one embodiment the gene signature consists of only *IFI44L* and *FAM89A*.

Surprisingly, the present inventors were able to discriminate subjects having a bacterial infection from subjects having a viral infection with a high sensitivity (above 90%) and specificity (above 96%) using a gene signature having only these 2 genes.

Accordingly, although the 2-gene signature comprising *IFI44L* and *FAM89A* can discriminate between bacterial and viral infections with a high degree of high sensitivity and specificity, additional genes can be included in the gene signature if required, for example one or more of the 36 genes may be employed and/or one of more housekeeping genes may be employed.

The skilled person has the ability to customise the gene signature from the pool of 36 genes and/or known genes as required. This allows the skilled person to balance the discriminatory power of the method against the cost and speed of the method by reducing or increasing the number of genes tested.

In one embodiment the gene signature consists of only *OAS1* and *EMR1*. In another embodiment the gene signature consists of only *IFI44L* and *IFI27*.

Thus in one embodiment the method further employs one or more housekeeping genes, such as 1, 2, 3, 4 or 5 housekeeping genes.

Housekeeping genes are not considered part of the signature in the context of the present specification.

Advantageously, in addition to a validation group (referred to herein as IRIS) the present inventors were also able to show that the disclosed method can accurately discriminate subjects having bacterial infections from subjects with viral infections or inflammatory disease in a meningococcal validation cohort, an inflammatory validation cohort, as well as in 3 published gene expression

datasets which compared bacterial infection with viral infection or inflammatory disease. Accordingly, the present inventors have demonstrated that the method is applicable across a wide range of different samples and patient groups which suggests that the method is robust and reliable.

In one embodiment the bacterial infection is selected from the group consisting of: *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*, *Clostridium tetani*, *Enterococcus faecalis*, *Enterococcus faecium*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, Group B streptococcus, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or acid fast bacteria such as *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycobacterium ulcerans*, *Mycobacterium avium intercellularae*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Brucella abortus*, *Brucella canis*, *Brucella melitensis*, *Brucella suis*, *Campylobacter jejuni*, *Escherichia coli*, *Francisella tularensis*, *Haemophilus influenzae*, *Helicobacter pylori*, *Legionella pneumophila*, *Leptospira interrogans*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Pseudomonas spp*, *Rickettsia rickettsii*, *Salmonella typhi*, *Salmonella typhimurium*, *Shigella sonnei*, *Treponema pallidum*, *Vibrio cholerae*, *Yersinia pestis*, *Kingella kingae*, *Stenotrophomonas* and *Klebsiella*.

In one embodiment the bacterial infection is a serious bacterial infection, for example bacterial meningitis, a respiratory infection, a urinary tract infection and/or bacteraemia.

In one embodiment the method of the present disclosure is capable of identifying a subject with bacterial infection in the presence of viral infection and/or an inflammatory disease.

In one embodiment the method of the present disclosure is capable of discriminating a subject with bacterial infection from a patient with viral infection and/or inflammatory disease only.

In one embodiment the viral infection is selected from the group comprising or consisting of: Influenza such as Influenza A, including but not limited to: H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, Influenza B and Influenza C, Respiratory Syncytial Virus (RSV), rhinovirus, enterovirus, bocavirus, parainfluenza, adenovirus, metapneumovirus, herpes simplex virus, Chickenpox virus, Human papillomavirus, Hepatitis, Epstein-Barr virus, Varicella-zoster virus, Human cytomegalovirus, Human herpesvirus, type 8 BK virus, JC virus, Smallpox, Parvovirus B19, Human astrovirus, Norwalk virus, coxsackievirus, poliovirus, Severe acute respiratory syndrome virus, yellow fever virus, dengue virus. West Nile virus. Rubella virus. Human immunodeficiency virus, Guanarito virus, Junin virus, Lassa virus, Machupo virus, Sabia virus, Crimean-Congo haemorrhagic fever virus, Ebola virus, Marburg virus, Measles virus, Mumps virus, Rabies virus and Rotavirus.

In one embodiment the inflammatory disease is disease is juvenile idiopathic arthritis (JIA), Henoch-Schönlein purpura (HSP) or systemic lupus erythematosus (SLE).

In a further aspect the present disclosure provides a method of treating a subject having a bacterial or viral infection after diagnosis employing the method herein.

In one embodiment the subject is a child, for example under 17 years of age, such as 2 to 59 months old.

In one embodiment the subject is an infant, for example in the age range 0 to 59 days.

In one embodiment the subject has fever, for example is a febrile patient.

In one embodiment the method of the present disclosure is employed on a patient derived sample, for example a blood sample.

In one embodiment the analysis of gene expression modulation employs a microarray.

In one embodiment the analysis of gene expression modulation employs PCR, such as RT-PCR.

5 In one embodiment the PCR is multiplex PCR.

In one embodiment the PCR is quantitative.

In one embodiment the primers employed in the PCR comprise a label or a combination of labels.

In one embodiment the label is fluorescent or coloured, for example the label is coloured beads.

10 In one embodiment the analysis of gene expression modulation employs dual colour reverse transcriptase multiplex ligation dependent probe amplification.

In one embodiment the gene expression modulation is detected by employing fluorescence spectroscopy.

In one embodiment the gene expression modulation is detected by employing colourimetric analysis.

15 In one embodiment the gene expression modulation is detected employing by impedance spectroscopy.

In one embodiment the method comprises the further step of prescribing a treatment for the subject based on the results of the analysis of the gene signature.

20 Thus, in one aspect there is provided a method of treating a patient by administering an anti-bacterial agent, such as an antibiotic, wherein the patient is characterised in that the patient has been identified as positive for bacterial infection by the method disclosed herein.

In one aspect, there is provided a method of determining whether to administer an anti-bacterial agent to a subject, such as an antibiotic, comprising the steps of: performing the method according to the present disclosure, and administering the anti-bacterial agent to the subject if the method indicates that the subject has a bacterial infection.

25 In one embodiment the anti-bacterial agent is an antibiotic, for example selected from the group comprising ceftobiprole, ceflaroline, clindamycin, dalbavancin, daptomycin, linezolid, oritavancin, tedizolid, telavancin, tigecycline, vancomycin, aminoglycosides, carbapenems, ceftazidime, ceftobiprole, fluoroquinolones, piperacillin/tazobactam, ticarcillin/clavulanic acid, streptogramins, such as amikacin, gentamicin, kanamycin, netilmicin, tobramycin, paromomycin, streptomycin, 30 geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem/cilastatin, meropenem, cefadroxil, cefazolin, cefalotin/cefalothin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, vancomycin, telavancin, dalbavancin, oritavancin, dalbavancin, oritavancin, clindamycin, 35 linomycin, daptomycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazilidone, linezolid, posizolid, radezolid, torezolid, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, nafcillin, oxacillin, penicillin G, penicillin V, piperacillin, temocillin, ticarcillin, amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, bacitracin, colistin, 40 polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silver sulfadiazine, sulfadimethoxine,

sulfasalazine, sulfisoxazole, trimethoprim-sulfamethoxazole, sulfonamidochrysoidine, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, clofazimine, dapson, capremycin, cycloserine, ethambutol, ethionamide, isoniazid, pyrazinamide, rifampicin, rifapentine, streptomycin, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, thiamphenicol, tigecycline, tinidazole and trimethoprim.

In another aspect there is provided a method of treating a patient by administering an anti-viral agent, such as an oseltamivir or peramivir, wherein the patient is characterised in that the patient has been identified as negative for a bacterial infection by the method disclosed herein.

In another aspect, there is provided a method of determining whether to administer an anti-viral agent to a subject, such as oseltamivir or peramivir, comprising the steps of: performing the method according to any one of the preceding claims, and administering the anti-viral agent to the subject if the method indicates that the subject has a viral infection.

Hence, the presently disclosed method can aid in the appropriate treatment of patients, such as febrile patients, for example where it is unclear if the fever is due to a bacterial infection, viral infection or both. This has the advantage of ensuring rapid and appropriate treatment without the need to wait for bacterial culture results. Importantly, this can help to ensure that antibiotics are only prescribed when the subject genuinely has a bacterial infection rather than a viral infection.

In one aspect of the disclosure, there is provided a set of primers for use in multiplex PCR, wherein the set of primers include nucleic acid sequences specific to a polynucleotide gene transcript from at least one gene from each of the following groups:

- a) *IFI44L, IFI27, IFIT1, RSAD2, IFIT3, OTOF, IFIT2, EPSTI1, SERPING1, OAS1, IFI6, HLA-DRB6, HBZ, HS.386275, EIF2AK2, IFIT1L, FCER1A, C21ORF7, GYPE, GYPB, HBM, EIF1AY, LOC649143, HBD, FBXO7* and *KCNMA1*; and
- b) *FAM89A, KCNMA1, MERTK, EBI3, UPB1, EMR1, PTPN20, TMEM119, SLPI, S100P* and *PI3*.

In one aspect of the disclosure, there is provided a set of primers for use in multiplex PCR wherein the set of primers includes nucleic acid sequences specific to a polynucleotide gene transcript for at least one gene from the group consisting of:

- a) *IFI44L, IFI27, IFIT1, RSAD2, IFIT3, OTOF, IFIT2, EPSTI1, OAS1, IFI6, HS.386275* and *EIF2AK2*; and optionally includes nucleic acid sequences specific to a polynucleotide gene transcript for one or more genes selected from the group consisting of:
- b) *FAM89A, KCNMA1, MERTK, EBI3, UPB1, EMR1, PTPN20, TMEM119, SLPI, S100P* and *PI3*.

In one embodiment, the set of primers includes nucleic acid sequences specific to a polynucleotide gene transcript for at least one gene from each of the following groups:

- a) *IFI44L, IFI27, IFIT1, RSAD2, IFIT3, OTOF, IFIT2, EPSTI1, OAS1, IFI6, HS.386275, EIF2AK2*; and
- b) *FAM89A, KCNMA1, MERTK, EBI3, UPB1, EMR1, PTPN20, TMEM119, SLPI, S100P* and *PI3*.

In one embodiment, the nucleic acid sequences in the set are for no more than a total of 10 genes or less, such as 5 genes, in particular 2, 3, 4 or 5 genes.

In one embodiment, the nucleic acid sequences in the set are for only *IFI44L* and *FAM89A*. In another embodiment, the nucleic acid sequences in the set are for only *OAS1* and *EMR1*. In another embodiment, the nucleic acid sequences in the set are for only *IFI44L* and *IFI27*.

In one embodiment, the gene transcript is RNA, for example mRNA.

In one embodiment, the set of primers includes one or more nucleic acids sequences specific to a gene transcript encoded *IFI44L*, for example the *IFI44L* sequence shown in SEQ ID NO: 1.

In one embodiment, the set of primers includes one or more nucleic acid sequences specific to *FAM89A*, for example the *FAM89A* sequence shown in SEQ ID NO: 2.

5 In one embodiment the primers for each gene are at least a pair of nucleic acid primer sequences.

In one embodiment the primer length is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100 bases in length.

10 In one embodiment at least one primer for each gene comprises a label.

In one embodiment the labels on the primers are independently selected from selected from a fluorescent label, a coloured label, and antibody, step tag, his tag.

In one embodiment each primer in a given pair of primers is labelled, for example where one label quenches the fluorescence of the other label when said labels are within proximity of each other.

15 Examples of suitable primer sequences are given in Table 8. Accordingly, in one embodiment the primers comprise or consist of the sequences given in any one of SEQ ID NOs: 3 to 40.

In one aspect, there is provided a point of care test for identifying bacterial infection in a subject comprising the set of primers as defined above. Advantageously, the presently disclosed test can be performed rapidly in as little as a couple of hours without the need for complex diagnostic or lab equipment. Accordingly, the presently disclosed method can be easily implemented as part of an existing patient care program in a hospital setting as well as in more resource poor settings such as in remote villages.

In one aspect, there is provided the use of a set of primers as defined above in an assay to detect bacterial infection in a sample, for example a blood sample.

25 In another aspect of the disclosure there is provided a gene chip consisting of probes for detecting the modulation in gene expression levels of *IFI44L* and *FAM89A*; and optionally probes for one or more genes selected from the group consisting of: *IFI27L*, *IFT11*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPST11*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In one embodiment the gene chip consists of probes for detecting the expression levels of *IFI44L* and *FAM89A*, for example Illumina transcript ID no. ILMN_9752 for *IFI44L* and Illumina transcript ID no. ILMN_21686 for *FAM89A*.

35 In another embodiment the gene chip consists of probes for detecting the expression levels of *OAS1* and *EMR1*, for example Illumina transcript ID no. ILMN_2717 for *OAS1* and ILMN_12984 for *EMR1*.

In another embodiment the gene chip consists of probes for detecting the expression levels of *OAS1* and *EMR1*, for example Illumina transcript ID no. ILMN_2717 for *OAS1* and ILMN_12984 for *EMR1*.

In another embodiment the gene chip consists of probes for detecting the expression levels of *IFI44L* and *IFI27*, for example Illumina transcript ID no. ILMN_9752 for *IFI44L* and ILMN_17548 for *IFI27*.

40 Advantageously, a chip with probes for just 2 genes is able to accurately and reliably differentiate between a sample, for example whole blood derived from a subject having a bacterial infection from

a sample derived from a subject having a viral infection. Such a chip can be cheaply produced, making the chip particularly suited for use in resource poor settings.

In a further embodiment the present disclosure includes use of a known or commercially available gene chip in the method of the present disclosure.

5 BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows an overview of the study. Figure 1A shows a flowchart depicting the overall flow of patients in the study showing patient recruitment and subsequent selection for microarray analysis. Febrile children with infections were recruited to the *Immunopathology of Respiratory, Inflammatory and Infectious Disease Study*, and were classified into diagnostic groups based on the symptoms shown in the flowchart in Figure 1B.

HC Healthy Control; JIA juvenile idiopathic arthritis; ILAR International League of Associations for Rheumatology; HSP Henoch-Schönlein Purpura; SLE Systemic Lupus Erythematosus; GEO Gene Expression Omnibus; DB Definite Bacterial; PB Probable Bacterial; U Unknown; PV Probable Viral; DV Definite Viral; CRP: C-reactive protein.

Figure 2 shows a flowchart depicting the overall study pipeline showing sample handling, derivation of test and training datasets, data processing, and analysis pipeline including application of 38-transcript elastic net classifier and 2-transcript DRS classifier, to the test set, the validation datasets and published (external) validation datasets.

DB Definite Bacterial; PB Probable Bacterial; U Unknown; PV Probable Viral; DV Definite Viral; HSP Henoch-Schönlein Purpura; JIA Juvenile Idiopathic Arthritis; SLE Systemic Lupus Erythematosus; HC Healthy Control; SDE Significantly Differentially Expressed; FC fold change; FS-PLS Forward Selection - Partial Least Squares; DRS Disease Risk Score.

Figure 3 shows a classification performance plot and Receiver Operating Characteristic (ROC) curve based on the 2-transcript DRS signature, applied to the Definite Bacterial and Viral groups of the 20% test set (A & B) and the IRIS validation dataset (C & D). Boxes show median with 25th and 75th quartiles; whiskers show ranges. Sensitivity, specificity, and AUC are reported in Table 5.

Figure 4 shows plots indicating the performance based on the DRS signature, applied to the indeterminate groups of Probable Bacterial, Probable Viral, and Unknown of the discovery (A) and IRIS validation (B) sets. Boxes show median with 25th and 75th quartiles; whiskers show ranges.

Figure 5 shows a graph indicating the proportion of patients in the combined test and validation group receiving antibiotics, and the proportion of positive bacterial calls, as predicted by DRS. The proportion of patients classified as bacterial by the DRS and the proportion receiving antibiotics were, respectively: 2.9% and 79.5% in the Definite Viral group; 28.6% and 70.0% in the Probable Viral group; 37.7% and 93.9% in the Unknown group; 65.3% and 100.0% in the Probable Bacterial group; and 96.4% and 100% in the Definite Bacterial groups.

Figure 6 shows a Principal Components analysis (PCA) of the samples in the discovery set (PC1 & PC2) based on all transcripts and samples in the discovery cohort after background adjustment and normalization. No sample was removed from the analysis at this stage. A confidence ellipse was calculated for the population mean and is shown in the plot (99%). Number of arrays for each sample are: Viral n=92, Probable Viral n=5, Unknown n=49, Probable Bacterial n=42, Bacterial n=52.

Figure 7 shows heatmaps indicating the clustering of the training and test datasets based on the bacterial vs. viral 28-transcript signature. Patients are represented as columns (dark grey are patients

with Definite Bacterial infection, light grey are patients with Definite Viral infection) and individual transcripts are shown in rows (transcripts shown in dark grey are up-regulated and those in light grey are down-regulated). The dendrograms for samples and transcripts are shown on the top and left of the heatmaps respectively, indicating hierarchical clusters of the data. Patients in the training set: Definite Bacterial n=42, Definite Viral n=92. Patients in the test set: Definite Bacterial n=10, Definite Viral n=19

Figure 8 shows Elastic net prediction value plots and Receiver Operating Characteristic (ROC) curves, based on the 38-transcript signature, applied to the Definite Bacterial and Definite Viral groups of the 80% training set (A & D), the 20% test set (B & E) and the IRIS validation dataset (C & F). Sensitivity, specificity and AUC are reported in Table 4. Boxes show median with 25th and 75th quartiles; whiskers show “range” (defined by *boxplot* function in R). With a “range” value set at 1, the whiskers extend no more than 1 times the interquartile range. The elastic net prediction value (the outcome variable Y obtained from fitting the elastic net model) can range from 0 (indicating viral infection) to 1 (indicating bacterial infection). Patients in the training set: Definite Bacterial n=42, Definite Viral n=92. Patients in the test set: Definite Bacterial n=10, Definite Viral n=19. Patients in IRIS validation dataset: Definite Bacterial n=23, Definite Viral n=28.

Figure 9 shows a classification performance plot (A) and a Receiver Operating Characteristic (ROC) curve (B), based on the 2-transcript DRS signature, applied to the Definite Bacterial and Viral groups of the 80% training dataset. Sensitivity, specificity and AUC are reported in Table 5. Boxes show median with 25th and 75th quartiles; whiskers show ranges. Patients in the training set: Definite Bacterial n=42, Definite Viral n=92.

Figure 10 shows a STARD flow diagram for assessment of diagnostic test accuracy in the test set (A) and validation set (B), including a 2x2 table of results comparing performance of the 2-transcript DRS against the clinical coding as bacterial or viral infection.

Figure 11 shows a principal component analysis of meningococcal and IRIS validation samples after merging with ComBat. The two-transcript DRS classifier was applied on external data, and its ability to discriminate between bacterial and non-bacterial patients was assessed. In the case of the meningococcal validation data set, there were no comparator non-bacterial patients, and in order to estimate the accuracy of the DRS signature, we employed the viral group of the IRIS validation dataset. The two datasets were merged using the ComBat method to remove non-biological experimental variation, using the healthy controls from both datasets as reference. The PCA plot of the merged dataset indicates successful removal of the batch effects. The healthy controls from the IRIS dataset (*HC_IRIS* n=16) and the healthy controls from the meningococcal dataset (*HC_Mening* n=21) are shown lying adjacent, as well as the bacterial patients from both datasets (*Bacterial_IRIS* n=23 and *Bacterial_Mening* n=24). The viral patients of the IRIS dataset lie between the bacterial patients and healthy controls (*Viral_IRIS* n=28). The 1st principal component was found to capture the differences in gene expression by infection status.

Figure 12 shows a classification performance plot (A) and a Receiver Operating Characteristic (ROC) curve (B), based on the 2-transcript DRS signature, applied to the gram-positive (IRIS validation), gram-negative (IRIS and meningococcal validation), and viral (IRIS validation) groups of the merged datasets. Boxes show median with 25th and 75th quartiles; whiskers show ranges.

Sensitivity, specificity and AUC are reported in Table 7, based on discrimination of gram-negative infection and viral infection. The bacterial gram-positive group is shown on Figure 12A for illustrative purposes.

Figure 13 shows classification performance plots and Receiver Operating Characteristic (ROC) curves, based on the 2-transcript DRS signature, applied to the inflammatory validation groups, JIA and HSP (A, B), and to 3 external published datasets: bacterial and inflammatory patients with systemic lupus erythematosus (C, D)[18]; bacterial and viral patients from the Ramilo *et al* study (E, F)[15]; and bacterial and viral patients from the Hu *et al* study (G, H)[12], and bacterial and viral adult patients from the Suarez *et al* study (I, J) [17]. Boxes show median with 25th and 75th quartiles; whiskers show ranges. Sensitivity, specificity and AUC are reported in Table 7.

Figure 14 shows the performance of the DRS in relation to severity of illness in the IRIS validation set. In order to investigate whether the severity of illness influenced the performance of the 2-transcript classifier, we analyzed the DRS values in the definite Viral and definite Bacterial groups by need for admission to the pediatric intensive care unit (PICU) during their illness (as shown in Figure 4B). The horizontal DRS threshold line separates patients predicted as bacterial (above the line) or viral (below the line) (A). The 2-transcript DRS classified patients as bacterial or viral irrespective of their requirement for intensive care. The classification performance and Receiver Operating Characteristic (ROC) curve, based on the 2-transcript DRS signature is shown for patients requiring intensive care (solid line) or not requiring intensive care (dotted line) (B).

Figure 15 shows the performance of the DRS in relation to day of illness in the IRIS validation set. In order to investigate whether the duration of illness influenced performance of the 2-transcript classifier, DRS values were plotted relative to the patient-reported day of illness (including symptomatic days before hospital admission) at the time of blood sampling. The horizontal DRS threshold line separates patients predicted as bacterial (above the line) and viral (below the line) (as shown on Figure 4B). With the exception of one patient (see arrow), all of the DB patients were above the DRS threshold, whilst all of the DV patients were below the DRS threshold. There was no correlation of illness day with DRS. The plot does not include a single patient with a long illness.

For coloured versions of the figures refer to Herberg *et al* [49], Distinction between bacterial and viral infection in children using a two-transcript host RNA signature (JAMA 2016)

Figure 16 shows the Disease Risk Score and Receiver Operating Characteristic (ROC) curves based on the 2-transcript signature (the combined *IFI44L* and *FAM89A* expression values). (A) Disease risk score for bacterial and viral infection groups. The dotted line indicates a disease risk score threshold of -3.79, determined by the point on the definite bacterial vs definite viral ROC curve that maximized sensitivity and specificity. This was used to calculate the quoted sensitivity and specificity. Boxes indicate the interquartile ranges and the median (bold line); whiskers represent 1 or less times the interquartile range. (B) ROC curves for proven bacterial infection group vs viral groups. Data are as reported in study by Mahajan *et al* [50]. Data points indicate the corresponding thresholds.

Figure 17 shows the results of the RNA-Seq experiment using the 2-transcript signature *IFI44L* and *FAM89A*. (A) number of bacterial (66) and viral patients (31), (B) Disease Risk Score, (C) ROC curve.

DETAILED DESCRIPTION

The 36 genes/38 transcripts shown in Table 4 or Table 8 is useful for identifying a bacterial infection or discriminating a bacterial infection from a viral infection or for discriminating a bacterial infection from an inflammatory disease, such as juvenile idiopathic arthritis (JIA), Henoch-Schönlein purpura (HSP) or systemic lupus erythematosus (SLE).

5 In one embodiment one probe is employed for detecting the modulation in gene expression of each gene, for example selected from the list of probes shown in Table 4 or Table 8.

In another embodiment, two or more probes are employed for detecting the modulation of each gene, for example selected from the list of probes shown in Table 4 or Table 8.

10 In one embodiment the method of the present disclosure is able to differentiate a bacterial infection from different conditions/diseases or infections, such as a viral infection which have similar clinical symptoms.

In one embodiment the method is for discriminating a subject having a bacterial infection from a subject having a viral infection.

15 In one embodiment the method is for discriminating a subject having a bacterial infection from a subject having an inflammatory disease

In one embodiment there is detected the gene expression levels of at least 95% of the genes in a signature such as 95, 96, 97, 98, 99 or 100% providing the signature retains the ability to detect/discriminate the relevant clinical status without significant loss of specificity and/or sensitivity. The details of the gene signature is given below.

20 In one embodiment the exact gene list, i.e. 100% of the genes in Table 4 or Table 8 is employed.

In one embodiment of the present disclosure the gene signature is the minimum set of genes required to optimally detect the infection or discriminate the disease, for example between a bacterial infection and a viral infection or between a bacterial infection and an inflammatory disease.

25 Optimally is intended to mean the smallest set of genes needed to discriminate between a bacterial infection and a viral infection or an inflammatory disease without significant loss of specificity and/or sensitivity of the signature's ability to detect or discriminate.

Detect or detecting as employed herein is intended to refer to the process of identifying a bacterial infection, a viral infection, or an inflammatory disease in a sample, in particular through detecting modulation of the relevant genes in the signature.

30 Discriminate refers to the ability of the signature to differentiate between different disease statuses, for example a bacterial infection vs a viral infection or a bacterial infection vs an inflammatory disease. Detect and discriminate are interchangeable in the context of the gene signature.

In one embodiment the method is able to discriminate between a bacterial infection and a viral infection or inflammatory disease in a subject derived sample.

35 Subject as employed herein is a human suspected of having a bacterial or viral infection from whom a sample is derived. The term patient may be used interchangeably although in one embodiment a patient has a morbidity.

40 In one embodiment the method of the present disclosure is performed on a sample derived from a subject having or suspected of having a bacterial infection, for example wherein the subject exhibits symptoms normally associated with a bacterial infection but not a viral infection.

In one embodiment the method of the present disclosure is performed on a sample derived from a subject having or suspected of having a viral infection, for example wherein the subject exhibits

symptoms normally associated with a viral infection but not a bacterial infection. Testing a sample from such a subject can help to identify a hidden bacterial infection.

In one embodiment the subject exhibits symptoms of a viral infection. In another embodiment the subject exhibits symptoms of a bacterial infection. In yet another embodiment the subject exhibits
5 symptoms of both a bacterial and a viral infection.

In one embodiment the method according to the present disclosure is performed on a subject having or suspected of having an acute infection, such as a severe/serious bacterial infection (SBI).

In a further embodiment the sample is a sample derived from a febrile subject; that is to say with a temperature above the normal body temperature of 37.5°C.

10 In yet a further embodiment the analysis is performed to establish if a fever is associated with a bacterial or viral infection. Establishing the source of the fever/infection advantageously allows the prescription and/or administration of appropriate medication, for example those with bacterial infections can be given antibiotics and those with viral infections can be given antipyretics.

Efficient treatment is advantageous because it minimises hospital stays, ensures that patients obtain
15 appropriate treatment, which may save lives, especially when the patient is an infant or child, and also ensures that resources are used appropriately.

In recent years it has become apparent that the over-use of antibiotics should be avoided because it leads to bacteria developing resistance. Therefore, the administration of antibiotics to patients who do not have bacterial infection should be avoided.

20 In one embodiment the subject is an adult. Adult is defined herein as a person of 18 years of age or older. The presently disclosed method is able to detect a bacterial infection in an adult, as well as discriminate between a bacterial infection and a viral infection. See for example Figure 13 (I and J) and Table 7.

In one embodiment the subject is a child. Child as employed herein refers to a person under the age
25 of 18, such as 5 to 17 years of age.

Modulation of gene expression as employed herein means up-regulation or down-regulation of a gene or genes.

Up-regulated as employed herein is intended to refer to a gene transcript which is expressed at
30 higher levels in a diseased or infected patient sample relative to, for example, a control sample free from a relevant disease or infection, or in a sample with latent disease or infection or a different stage of the disease or infection, as appropriate.

Down-regulated as employed herein is intended to refer to a gene transcript which is expressed at
35 lower levels in a diseased or infected patient sample relative to, for example, a control sample free from a relevant disease or infection or in a sample with latent disease or infection or a different stage of the disease or infection.

The modulation is measured by measuring levels of gene expression by an appropriate technique.

Gene expression as employed herein is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as ribosomal RNA (rRNA), transfer RNA (tRNA) or small nuclear RNA (snRNA) genes, the
40 product is a functional RNA. That is to say, RNA with a function.

Gene expression data as employed herein is intended to refer to any data generated from a patient sample that is indicative of the expression of the two or more genes, for example 3, 4, 5, 6, 7, 8, 9, 10,

11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50.

In one embodiment one or more, for example 1 to 21, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20, genes are replaced by a gene with an equivalent function provided the signature retains the ability to detect/discriminate the relevant clinical status without significant loss in specificity and/or sensitivity.

In one embodiment the genes employed have identity with genes listed in the relevant tables, such as Table 4.

In one embodiment, one or more of the genes in the 36 gene signature are significantly differentially expressed in a sample derived from a subject having a bacterial infection compared to a sample derived from a subject having a viral infection or an inflammatory disease.

Gene signature as used herein is intended to refer to two or more genes which when tested together are able to detect/discriminate the relevant clinical status. Hence, a gene signature represents a minimal set of genes which have sufficient discriminatory power to identify a subject having a bacterial infection or to discriminate a subject having bacterial infection from a subject having a viral infection or inflammatory disease.

In one embodiment the gene signature is based on two genes of primary importance. Of primary importance as used herein means that the gene expression levels of the two genes is representative of the gene expression levels of other genes. For example, the expression levels of the first gene of primary importance may be highly correlated with the expression levels of a first group of genes, whilst the expression levels of the second gene of primary importance may be highly correlated with the expression levels of a second group of genes.

Therefore, each gene of primary importance may be used as a representative of the other highly correlated genes from their respective groups, thereby eliminating the need to test all of genes within each group. In other words, testing the expression levels of just the two genes of primary importance provides a similar sensitivity and/or specificity as testing the expression levels of all of the genes.

Significantly differentially expressed as employed herein means the gene shows a log₂ fold change >0.5 or <-0.5 in a sample derived from a subject having a bacterial infection compared to a sample derived from a subject having a viral infection or an inflammatory disease.

In one embodiment, up-regulated as used herein means the gene shows a log₂ fold change >0.5.

In one embodiment, down-regulated as used herein means the gene shows a log₂ fold change <-0.5.

In one embodiment, one or more of the following genes are down-regulated in a subject having a bacterial infection: *IFI27*, *IFI44L*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7* and *KCNMA1*.

In one embodiment, one or more of the following genes are up-regulated in a subject having a viral infection or an inflammatory disease: *IFI27*, *IFI44L*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD* and *FBXO7*.

In one embodiment, one or more of the following genes are up-regulated in a subject having a bacterial infection: *KCNMA1*, *MERTK*, *EBI3*, *FAM89A*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In one embodiment, one or more of the following genes are down-regulated in a subject having a viral infection or an inflammatory disease: *KCNMA1*, *MERTK*, *EBI3*, *FAM89A*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

5 In one embodiment, one or more of the following genes are down-regulated in a subject having a bacterial infection: *IFI27*, *IFI44L*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7* and *KCNMA1*; and one or more of the following genes are up-regulated: *KCNMA1*, *MERTK*, *EBI3*, *FAM89A*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

10 In one embodiment, one or more of the following genes are up-regulated in a subject having a viral infection or an inflammatory disease: *IFI27*, *IFI44L*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7* and *KCNMA1*; and one or more of the following genes are down-regulated: *KCNMA1*, *MERTK*, *EBI3*, *FAM89A*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

15 "Presented in the form of" as employed herein refers to the laying down of genes from one or more of the signatures in the form of probes on a microarray.

Accurately and robustly as employed herein refers to the fact that the method can be employed in a practical setting or low resource setting, such as Africa, and that the results of performing the method properly give a high level of confidence that a true result is obtained.

20 High confidence is provided by the method when it provides few results that are false positives (e.g. the result suggests that the subject has a bacterial infection when he/she does not) and also has few false negatives (e.g. the result suggests that the subject does not have a bacterial infection when he/she does).

25 High confidence would include 90% or greater confidence, such as 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100% confidence when an appropriate statistical test is employed.

In one embodiment the method provides a sensitivity of 80% or greater such as 90% or greater in particular 95% or greater, for example where the sensitivity is calculated as below:

$$\text{sensitivity} = \frac{\text{number of true positives}}{\text{number of true positives} + \text{number of false negatives}}$$

$$= \text{probability of a positive test given that the patient is ill}$$

30 In one embodiment the method provides a high level of specificity, for example 80% or greater such as 90% or greater in particular 95% or greater, for example where specificity is calculated as shown below:

$$\text{specificity} = \frac{\text{number of true negatives}}{\text{number of true negatives} + \text{number of false positives}}$$

$$= \text{probability of a negative test given that the patient is well}$$

In one embodiment the sensitivity of method of the 38 transcript gene signature is 90 to 100%, such as 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%.

35 In one embodiment the specificity of the method of the 38 transcript gene signature is 85 to 100%, such as 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%.

In one embodiment the sensitivity of the method of the 2 transcript gene signature is 85 to 100%, such as 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%.

In one embodiment the specificity of the method of the 2 transcript gene signature is 85 to 100%, such as 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99%.

- 5 There are a number of ways in which gene expression can be measured including microarrays, tiling arrays, DNA or RNA arrays for example on gene chips, RNA-seq and serial analysis of gene expression. Any suitable method of measuring gene modulation may be employed in the method of the present disclosure.

10 In one embodiment the gene expression measured is that of the host (e.g. human), for example the host inflammatory response, i.e. not that of the infectious agent or disease.

In one embodiment the method according to the present disclosure may be employed to detect a bacterial infection, such as *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Chlamydophila psittaci*, *Mycoplasma pneumoniae*.

15 In one embodiment the disclosed method may be employed to detect a serious/severe bacterial infection (SBI), including but not limited to bacterial meningitis such as acute bacterial meningitis, septicaemia, acute respiratory infections such as tuberculosis, tuberculosis meningitis, whipple disease, nocardiosis, urinary tract infections, bacteraemia and acute cystitis.

20 In one embodiment the method according to the present disclosure may be employed to detect a Gram positive bacterial infection, such as but not limited to *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*, *Clostridium tetani*, *Enterococcus faecalis*, *Enterococcus faecium*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Group B streptococcus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or acid fast bacteria such as *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycobacterium ulcerans* and *Mycobacterium avium intercellularae*.

25 In one embodiment the method according to the present disclosure may be employed to detect a Gram negative bacterial infection, such as but not limited to *Bordetella pertussis*, *Borrelia burgdorferi*, *Brucella abortus*, *Brucella canis*, *Brucella melitensis*, *Brucella suis*, *Campylobacter jejuni*, *Escherichia coli*, *Francisella tularensis*, *Haemophilus influenzae*, *Helicobacter pylori*, *Legionella pneumophila*, *Leptospira interrogans*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Pseudomonas spp*, *Rickettsia rickettsii*, *Salmonella typhi*, *Salmonella typhimurium*, *Shigella sonnei*, *Treponema pallidum*, *Vibrio cholerae*, *Yersinia pestis*, *Kingella kingae*, *Stenotrophomonas* and *Klebsiella*.

35 In one embodiment the method according to the present disclosure may be employed to detect a viral infection for example, Influenza such as Influenza A, including but not limited to: H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, Influenza B and Influenza C, Respiratory Syncytial Virus (RSV), rhinovirus, enterovirus, bocavirus, parainfluenza, adenovirus, metapneumovirus, herpes simplex virus, Chickenpox virus, Human papillomavirus, Hepatitis, Epstein-Barr virus, Varicella-zoster virus, Human cytomegalovirus, Human herpesvirus, type 8 BK virus, JC virus, Smallpox, Parvovirus B19, Human astrovirus, Norwalk virus, coxsackievirus, poliovirus, Severe acute
40 respiratory syndrome virus, yellow fever virus, dengue virus. West Nile virus. Rubella virus. Human immunodeficiency virus, Guanarito virus, Junin virus, Lassa virus, Machupo virus, Sabia virus,

Crimean-Congo haemorrhagic fever virus, Ebola virus, Marburg virus, Measles virus, Mumps virus, Rabies virus and Rotavirus.

In one embodiment the method according to the present disclosure may be employed to detect an inflammatory disease such as juvenile idiopathic arthritis (JIA), Henoch-Schönlein purpura (HSP) or systemic lupus erythematosus (SLE). Other examples of inflammatory diseases include asthma, chronic peptic ulcer, tuberculosis, rheumatoid arthritis, chronic periodontitis, ulcerative colitis, Crohn's disease, chronic sinusitis, chronic active hepatitis, celiac disease and vasculitis.

In one embodiment DNA or RNA from the subject sample is analysed.

In one embodiment RNA from the subject sample is analysed.

In one embodiment mRNA from the subject sample is analysed.

In one embodiment the sample is solid or fluid, for example blood or serum or a processed form of any one of the same.

A fluid sample as employed herein refers to liquids originating from inside the bodies of living people. They include fluids that are excreted or secreted from the body as well as body water that normally is not. Includes amniotic fluid, aqueous humour and vitreous humour, bile, blood serum, breast milk, cerebrospinal fluid, cerumen (earwax), chyle, endolymph and perilymph, gastric juice, mucus (including nasal drainage and phlegm), sputum, peritoneal fluid, pleural fluid, saliva, sebum (skin oil), semen, sweat, tears, vaginal secretion, vomit, urine. Particularly blood and serum.

Blood as employed herein refers to whole blood, that is serum, blood cells and clotting factors, typically peripheral whole blood.

Serum as employed herein refers to the component of whole blood that is not blood cells or clotting factors. It is plasma with fibrinogens removed.

In one embodiment the subject derived sample is a blood sample.

In one embodiment the sample is whole blood. Hence in one embodiment the RNA sample is derived from whole blood.

The RNA sample may be subjected to further amplification by PCR, such as whole genome amplification in order to increase the amount of starting RNA template available for analysis. Alternatively, the RNA sample may be converted into cDNA by reverse transcriptase, such as HIV-1 reverse transcriptase, moloney murine leukaemia virus (M-MLV) reverse transcriptase, AMV reverse transcriptase and telomerase reverse transcriptase. Such amplification steps may be necessary for smaller sample volumes, such as blood samples obtained from children.

In one or more embodiments the analysis is *ex vivo*.

Ex vivo as employed herein means that which takes place outside the body.

In one embodiment the gene expression data is generated from a microarray, such as a gene chip.

Microarray as employed herein includes RNA or DNA arrays, such as RNA arrays.

Polymerase chain reaction (PCR) as employed herein refers to a widely used molecular technique to make multiple copies of a target DNA sequence. The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers containing sequences complementary to the target region along with a DNA polymerase, which the method is named after, are key components to enable selective and repeated amplification. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the DNA template is exponentially amplified.

Multiplex PCR as employed herein refers to the use of a polymerase chain reaction (PCR) to amplify two or more different DNA sequences simultaneously, i.e. as if performing many separate PCR reactions together in one reaction.

Primer as employed herein is intended to refer to a short strand of nucleic acid sequence, usually a chemically synthesised oligonucleotide, which serve as a starting point for DNA synthesis reactions. Primers are typically about 15 base pairs long but can vary from 5 to 100 bases long. It is required in processes such as PCR because DNA polymerases can only add new nucleotides or base pairs to an existing strand of DNA. During a PCR reaction, the primer hybridises to its complementary sequence in a DNA sample. Next, DNA polymerase starts replication at the 3' end of the primer and extends the primer by copying the sequence of the opposite DNA strand.

In one embodiment the primers of the present disclosure are specific for RNA, such as mRNA, i.e. they are complementary to RNA sequences. In another embodiment, the primers are specific for cDNA, i.e. they are complementary to cDNA sequences.

In one embodiment the primers of the present disclosure comprise a label which enables the primers to be detected or isolated. Examples of labels include but are not limited to a fluorescent label, a coloured label, and antibody, step tag, his tag.

In another embodiment, each primer in a given pair of primers is labelled, for example where one label (also known as a quencher) quenches the fluorescence of the other label when said labels are within proximity of each other. Such labels are particularly useful in real time PCR reactions for example. Examples of such label pairs include 6-carboxyfluorescein (FAM) and tetrachlorofluorescein, or tetramethylrhodamine and tetrachlorofluorescein.

Point of care test or bedside test as used herein is intended to refer to a medical diagnostic test which is conducted at or near the point of care, i.e. at the time and place of patient care. This is in contrast with a conventional diagnostic test which is typically confined to the medical laboratory and involves sending specimens away from the point of care to the laboratory for testing. Such diagnostic tests often require many hours or days before the results of the test can be received. In the meantime, patient care must continue without knowledge of the test results. In comparison, a point of care test is typically a simple medical test that can be performed rapidly.

A gene chip is essentially a microarray that is to say an array of discrete regions, typically nucleic acids, which are separate from one another and are, for example arrayed at a density of between, about 100/cm² to 1000/cm², but can be arrayed at greater densities such as 10000/cm².

The principle of a microarray experiment, is that mRNA from a given cell line or tissue is used to generate a labelled sample typically labelled cDNA or cRNA, termed the 'target', which is hybridised in parallel to a large number of, nucleic acid sequences, typically DNA or RNA sequences, immobilised on a solid surface in an ordered array. Tens of thousands of transcript species can be detected and quantified simultaneously. Although many different microarray systems have been developed the most commonly used systems today can be divided into two groups.

Using this technique, arrays consisting of more than 30,000 cDNAs can be fitted onto the surface of a conventional microscope slide. For oligonucleotide arrays, short 20-25mers are synthesised in situ, either by photolithography onto silicon wafers (high-density-oligonucleotide arrays from Affymetrix) or by ink-jet technology (developed by Rosetta Inpharmatics and licensed to Agilent Technologies).

Alternatively, pre-synthesised oligonucleotides can be printed onto glass slides. Methods based on synthetic oligonucleotides offer the advantage that because sequence information alone is sufficient to generate the DNA to be arrayed, no time-consuming handling of cDNA resources is required. Also, probes can be designed to represent the most unique part of a given transcript, making the detection of closely related genes or splice variants possible. Although short oligonucleotides may result in less specific hybridization and reduced sensitivity, the arraying of pre-synthesised longer oligonucleotides (50-100mers) has recently been developed to counteract these disadvantages.

In one embodiment the gene chip is an off the shelf, commercially available chip, for example HumanHT-12 v4 Expression BeadChip Kit, available from Illumina, NimbleGen microarrays from Roche, Agilent, Eppendorf and Genechips from Affymetrix such as HU-UI 33.Plus 2.0 gene chips.

In an alternate embodiment the gene chip employed in the present invention is a bespoke gene chip, that is to say the chip contains only the target genes which are relevant to the desired profile. Custom made chips can be purchased from companies such as Roche, Affymetrix and the like. In yet a further embodiment the bespoke gene chip comprises a minimal disease specific transcript set.

In one embodiment the chip consists of probes for detecting the expression levels of 95-100% of the 36 genes listed in Table 4.

In one embodiment the chip consists of 95-100% of the 38 transcript probes listed in Table 4 or 8.

In one embodiment the gene chip consisting of probes for detecting the modulation in gene expression levels of at least 95% of the genes selected from the group consisting of: *IFI44L*, *FAM89A*, *IFI27L*, *IFT11*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In one embodiment the chip consists of all the 38 Illumina probes (i.e. 100% of the probes) listed in Table 4 or Table 8.

In one embodiment the following Illumina transcript ID nos. are used to detect the modulation in gene expression levels: ILMN_9752 for *IFI44L*, ILMN_21686 and/or ILMN_21686 for *FAM89A*, ILMN_17548 for *IFI27L*, ILMN_1751 for *IFT11*, ILMN_37168 for *RSAD2*, ILMN_22925 and/or ILMN_1944 for *IFIT3*, ILMN_27303 for *OTOF*, ILMN_28123 for *IFIT2*, ILMN_27754 for *EPSTI1*, ILMN_15074 for *SERPING1*, ILMN_2717 for *OAS1*, ILMN_13978 for *IFI6*, ILMN_5312 for *HLA-DRB6*, ILMN_19775 for *HBZ*, ILMN_89157 for *HS.386275*, ILMN_168435 for *EIF2AK2*, ILMN_5646 for *IFIT1L*, ILMN_18288 for *FCER1A*, ILMN_9078 for *C21ORF7*, ILMN_21264 for *GYPE*, ILMN_27651 for *GYPB*, ILMN_2819 for *HBM*, ILMN_14704 for *EIF1AY*, ILMN_43805 for *LOC649143*, ILMN_9543 for *HBD*, ILMN_28646 for *FBXO7*, ILMN_24236 for *KCNMA1*, ILMN_173016 for *MERTK*, ILMN_23396 for *EBI3*, ILMN_9777 for *UPB1*, ILMN_12984 for *EMR1*, ILMN_137356 for *PTPN20*, ILMN_30233 for *TMEM119*, ILMN_28045 for *SLPI*, ILMN_23476 for *S100P* and ILMN_13685 for *PI3*.

In another embodiment Illumina transcript ID nos. ILMN_21686 and ILMN_21686 are both used to detect the modulation in gene expression levels of *FAM89A*, and Illumina transcript ID nos. ILMN_22925 and ILMN_1944 are used to detect the gene expression levels of *IFIT3*.

In one embodiment the chip consists of probes for detecting the expression levels of *IFI44L* and *FAM89A* and probes for detecting one or more of the remaining 34 genes listed in Table 4.

In one embodiment the chip consists of Illumina transcript ID no. ILMN_9752 for detecting the expression levels of *IFI44L* and Illumina transcript ID no. ILMN_21686 for detecting the expression

levels of *FAM89*, as well as one or more of the remaining 36 Illumina probes for detecting the expression levels of the 38 transcripts listed in Table 4 or Table 8.

In one embodiment the chip consisting of probes for detecting the modulation in gene expression levels of *IFI44L* and *FAM89A*; and optionally probes for one or more genes selected from the group consisting of: *IFI27L*, *IFT11*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.

In one embodiment the chip consists of probes for detecting the expression levels of only *IFI44L* and *FAM89A*. For example, the chip consists of Illumina transcript ID no. ILMN_9752 for *IFI44L* and Illumina transcript ID no. ILMN_21686 for *FAM89A*.

In one or more embodiments above, the chip may further include 1 or more, such as 1 to 10, house-keeping genes.

In one embodiment the gene expression data is generated in solution using appropriate probes for the relevant genes.

Probe as employed herein is intended to refer to a hybridisation probe which is a fragment of DNA or RNA of variable length (usually 100-1000 bases long) which is used in DNA or RNA samples to detect the presence of nucleotide sequences (the DNA target) that are complementary to the sequence in the probe. The probe thereby hybridises to single-stranded nucleic acid (DNA or RNA) whose base sequence allows probe-target base pairing due to complementarity between the probe and target.

In one embodiment the method according to the present disclosure and for example chips employed therein may comprise one or more house-keeping genes.

House-keeping genes as employed herein is intended to refer to genes that are not directly relevant to the profile for identifying the disease or infection but are useful for statistical purposes and/or quality control purposes, for example they may assist with normalising the data, in particular a house-keeping gene is a constitutive gene i.e. one that is transcribed at a relatively constant level. The housekeeping gene's products are typically needed for maintenance of the cell.

Examples of housekeeping genes include but are not limited to actin, *GAPDH*, ubiquitin, 18s rRNA, *RPII* (*POLR2A*), *TBP*, *PPIA*, *GUSB*, *HSPCB*, *YWHAZ*, *SDHA*, *RPS13*, *HPRT1* and *B4GALT6*.

In one embodiment minimal disease specific transcript set as employed herein means the minimum number of genes need to robustly identify the target disease state.

Minimal discriminatory gene set is interchangeable with minimal disease specific transcript set or minimal gene signature.

Normalising as employed herein is intended to refer to statistically accounting for background noise by comparison of data to control data, such as the level of fluorescence of house-keeping genes, for example fluorescent scanned data may be normalized using RMA to allow comparisons between individual chips. Irizarry et al 2003 describes this method.

Scaling as employed herein refers to boosting the contribution of specific genes which are expressed at low levels or have a high fold change but still relatively low fluorescence such that their contribution to the diagnostic signature is increased.

Fold change is often used in analysis of gene expression data in microarray and RNA-Seq experiments, for measuring change in the expression level of a gene and is calculated simply as the

ratio of the final value to the initial value i.e. if the initial value is A and final value is B, the fold change is B/A. Tusher et al 2001.

In programs such as Arrayminer, fold change of gene expression can be calculated. The statistical value attached to the fold change is calculated and is the more significant in genes where the level of expression is less variable between subjects in different groups and, for example where the difference between groups is larger.

The step of obtaining a suitable sample from the subject is a routine technique, which involves taking a blood sample. This process presents little risk to donors and does not need to be performed by a doctor but can be performed by appropriately trained support staff. In one embodiment the sample derived from the subject is approximately 2.5 ml of blood, however smaller volumes can be used for example 0.5-1ml.

Blood or other tissue fluids are immediately placed in an RNA stabilizing buffer such as included in the Pax gene tubes, or Tempus tubes.

If storage is required then it should usually be frozen within 3 hours of collections at -80°C.

In one embodiment the gene expression data is generated from RNA levels in the sample.

For microarray analysis the blood may be processed using a suitable product, such as PAX gene blood RNA extraction kits (Qiagen).

Total RNA may also be purified using the Tripure method - Tripure extraction (Roche Cat. No. 1 667 165). The manufacturer's protocols may be followed. This purification may then be followed by the use of an RNeasy Mini kit - clean-up protocol with DNase treatment (Qiagen Cat. No. 74106).

Quantification of RNA may be completed using optical density at 260nm and Quant-IT RiboGreen RNA assay kit (Invitrogen - Molecular probes RI 1490). The Quality of the 28s and 18s ribosomal RNA peaks can be assessed by use of the Agilent bioanalyser.

In another embodiment the method further comprises the step of amplifying the RNA. Amplification may be performed using a suitable kit, for example TotalPrep RNA Amplification kits (Applied Biosystems).

In one embodiment an amplification method may be used in conjunction with the labelling of the RNA for microarray analysis. The Nugen 3' ovation biotin kit (Cat: 2300-12, 2300-60).

The RNA derived from the subject sample is then hybridised to the relevant probes, for example which may be located on a chip. After hybridisation and washing, where appropriate, analysis with an appropriate instrument is performed.

In performing an analysis to ascertain whether a subject presents a gene signature indicative of disease or infection according to the present disclosure, the following steps are performed: obtain mRNA from the sample and prepare nucleic acids targets, hybridise to the array under appropriate conditions, typically as suggested by the manufactures of the microarray (suitably stringent hybridisation conditions such as 3X SSC, 0.1% SDS, at 50 <0>C) to bind corresponding probes on the array, and wash if necessary to remove unbound nucleic acid targets and analyse the results.

In one embodiment the readout from the analysis is fluorescence.

In one embodiment the readout from the analysis is colorimetric.

In one embodiment physical detection methods, such as changes in electrical impedance, nanowire technology or microfluidics may be used.

In one embodiment there is provided a method which further comprises the step of quantifying RNA from the subject sample.

If a quality control step is desired, software such as Genome Studio software may be employed.

Numeric value as employed herein is intended to refer to a number obtained for each relevant gene, from the analysis or readout of the gene expression, for example the fluorescence or colorimetric analysis. The numeric value obtained from the initial analysis may be manipulated, corrected and if the result of the processing is still a number then it will be continue to be a numeric value.

By converting is meant processing of a negative numeric value to make it into a positive value or processing of a positive numeric value to make it into a negative value by simple conversion of a positive sign to a negative or vice versa.

Analysis of the subject-derived sample will for the genes analysed will give a range of numeric values some of which are positive (preceded by + and in mathematical terms considered greater than zero) and some of which are negative (preceded by - and in strict mathematical terms are considered to less than zero). The positive and negative in the context of gene expression analysis is a convenient mechanism for representing genes which are up-regulated and genes which are down regulated.

In the method of the present disclosure either all the numeric values of genes which are down-regulated and represented by a negative number are converted to the corresponding positive number (i.e. by simply changing the sign) for example -1 would be converted to 1 or all the positive numeric values for the up-regulated genes are converted to the corresponding negative number.

The present inventors have established that this step of rendering the numeric values for the gene expressions positive or alternatively all negative allows the summing of the values to obtain a single value that is indicative of the presence of disease or infection or the absence of the same.

This is a huge simplification of the processing of gene expression data and represents a practical step forward thereby rendering the method suitable for routine use in the clinic.

By discriminatory power is meant the ability to distinguish between a bacterial infected and a viral infected sample/subject or between a bacterial infection and an inflammatory disease, such as SLE, JIA and HSP.

The discriminatory power of the method according to the present disclosure may, for example, be increased by attaching greater weighting to genes which are more significant in the signature, even if they are expressed at low or lower absolute levels.

As employed herein, raw numeric value is intended to, for example refer to unprocessed fluorescent values from the gene chip, either absolute fluorescence or relative to a house keeping gene or genes. Summing as employed herein is intended to refer to act or process of adding numerical values.

Composite expression score as employed herein means the sum (aggregate number) of all the individual numerical values generated for the relevant genes by the analysis, for example the sum of the fluorescence data for all the relevant up and down regulated genes. The score may or may not be normalised and/or scaled and/or weighted.

In one embodiment the composite expression score is normalised.

In one embodiment the composite expression score is scaled.

In one embodiment the composite expression score is weighted.

Weighted or statistically weighted as employed herein is intended to refer to the relevant value being adjusted to more appropriately reflect its contribution to the signature.

In one embodiment the method employs a simplified risk score as employed in the examples herein. Simplified risk score is also known as disease risk score (DRS).

Control as employed herein is intended to refer to a positive (control) sample and/or a negative (control) sample which, for example is used to compare the subject sample to, and/or a numerical value or numerical range which has been defined to allow the subject sample to be designated as positive or negative for disease/infection by reference thereto.

Positive control sample as employed herein is a sample known to be positive for the pathogen or disease in relation to which the analysis is being performed, such as a bacterial infection.

Negative control sample as employed herein is intended to refer to a sample known to be negative for the pathogen or disease in relation to which the analysis is being performed.

In one embodiment the control is a sample, for example a positive control sample or a negative control sample, such as a negative control sample.

In one embodiment the control is a numerical value, such as a numerical range, for example a statistically determined range obtained from an adequate sample size defining the cut-offs for accurate distinction of disease cases from controls.

Conversion of multi-gene transcript disease signatures into a single number disease score

Once the RNA expression signature of the disease has been identified by variable selection, the transcripts are separated based on their up- or down-regulation relative to the comparator group. The two groups of transcripts are selected and collated separately.

Summation of up-regulated and down-regulated RNA transcripts

To identify the single disease risk score for any individual patient, the raw intensities, for example fluorescent intensities (either absolute or relative to housekeeping standards) of all the up-regulated RNA transcripts associated with the disease are summated. Similarly summation of all down-regulated transcripts for each individual is achieved by combining the raw values (for example fluorescence) for each transcript relative to the unchanged housekeeping gene standards. Since the transcripts have various levels of expression and respectively their fold changes differ as well, instead of summing the raw expression values, they can be scaled and normalised between 0,1. Alternatively they can be weighted to allow important genes to carry greater effect. Then, for every sample the expression values of the signature's transcripts are summated, separately for the up- and down- regulated transcripts.

The total disease score incorporating the summated fluorescence of up- and down-regulated genes is calculated by adding the summated score of the down-regulated transcripts (after conversion to a positive number) to the summated score of the up-regulated transcripts, to give a single number composite expression score. This score maximally distinguishes the cases and controls and reflects the contribution of the up- and down- regulated transcripts to this distinction.

Comparison of the disease risk score in cases and controls

The composite expression scores for patients and the comparator group may be compared, in order to derive the means and variance of the groups, from which statistical cut-offs are defined for accurate distinction of cases from controls. Using the disease subjects and comparator populations, sensitivities and specificities for the disease risk score may be calculated using, for example a Support Vector Machine and internal elastic net classification.

Disease risk score as employed herein is an indicator of the likelihood that patient has a bacterial infection when comparing their composite expression score to the comparator group's composite expression score.

Development of the disease risk score into a simple clinical test for disease severity or disease risk prediction

The approach outlined above in which complex RNA expression signatures of disease or disease processes are converted into a single score which predicts disease risk can be used to develop simple, cheap and clinically applicable tests for disease diagnosis or risk prediction.

The procedure is as follows: For tests based on differential gene expression between cases and controls (or between different categories of cases such as severity), the up- and down-regulated transcripts identified as relevant may be printed onto a suitable solid surface such as microarray slide, bead, tube or well.

Up-regulated transcripts may be co-located separately from down-regulated transcripts either in separate wells or separate tubes. A panel of unchanged housekeeping genes may also be printed separately for normalisation of the results.

RNA recovered from individual patients using standard recovery and quantification methods (with or without amplification) is hybridised to the pools of up- and down-regulated transcripts and the unchanged housekeeping transcripts.

Control RNA is hybridised in parallel to the same pools of up- or down-regulated transcripts.

Total value, for example fluorescence for the subject sample and optionally the control sample is then read for up- and down-regulated transcripts and the results combined to give a composite expression score for patients and controls, which is/are then compared with a reference range of a suitable number of healthy controls or comparator subjects.

Correcting the detected signal for the relative abundance of RNA species in the subject sample

The details above explain how a complex signature of many transcripts can be reduced to the minimum set that is maximally able to distinguish between patients and other phenotypes. For example, within the up-regulated transcript set, there will be some transcripts that have a total level of expression many fold lower than that of others. However, these transcripts may be highly discriminatory despite their overall low level of expression. The weighting derived from the elastic net coefficient can be included in the test, in a number of different ways. Firstly, the number of copies of individual transcripts included in the assay can be varied. Secondly, in order to ensure that the signal from rare, important transcripts are not swamped by that from transcripts expressed at a higher level, one option would be to select probes for a test that are neither overly strongly nor too weakly expressed, so that the contribution of multiple probes is maximised. Alternatively, it may be possible to adjust the signal from low-abundance transcripts by a scaling factor.

Whilst this can be done at the analysis stage using current transcriptomic technology as each signal is measured separately, in a simple colorimetric test only the total colour change will be measured, and it would not therefore be possible to scale the signal from selected transcripts. This problem can be circumnavigated by reversing the chemistry usually associated with arrays. In conventional array chemistry, the probes are coupled to a solid surface, and the amount of biotin-labelled, patient-derived target that binds is measured. Instead, we propose coupling the biotin-labelled cRNA derived from the patient to an avidin-coated surface, and then adding DNA probes coupled to a chromogenic

enzyme via an adaptor system. At the design and manufacturing stage, probes for low-abundance but important transcripts are coupled to greater numbers, or more potent forms of the chromogenic enzyme, allowing the signal for these transcripts to be 'scaled-up' within the final single-channel colorimetric readout. This approach would be used to normalise the relative input from each probe in the up-regulated, down-regulated and housekeeping channels of the kit, so that each probe makes an appropriately weighted contribution to the final reading, which may take account of its discriminatory power, suggested by the weights of variable selection methods.

The detection system for measuring multiple up or down regulated genes may also be adapted to use rTPCR to detect the transcripts comprising the diagnostic signature, with summation of the separate pooled values for up and down regulated transcripts, or physical detection methods such as changes in electrical impedance. In this approach, the transcripts in question are printed on nanowire surfaces or within microfluidic cartridges, and binding of the corresponding ligand for each transcript is detected by changes in impedance or other physical detection system

In one embodiment the gene chip is a fluorescent gene chip that is to say the readout is fluorescence. Fluorescence as employed herein refers to the emission of light by a substance that has absorbed light or other electromagnetic radiation.

Thus in an alternate embodiment the gene chip is a colorimetric gene chip, for example colorimetric gene chip uses microarray technology wherein avidin is used to attach enzymes such as peroxidase or other chromogenic substrates to the biotin probe currently used to attach fluorescent markers to DNA. The present disclosure extends to a microarray chip adapted to be read by colorimetric analysis and adapted to discriminate a subject having a bacterial infection from a subject having a viral infection or an inflammatory disease. The present disclosure also extends to use of a colorimetric chip to analyse a subject sample for discriminating a subject having a bacterial infection from a subject having a viral infection or an inflammatory disease.

Colorimetric as employed herein refers to as assay wherein the output is in the human visible spectrum.

In an alternative embodiment, a gene set or probe set for discriminating a subject having a bacterial infection from a subject having a viral infection or an inflammatory disease may be detected by physical detection methods including nanowire technology, changes in electrical impedance, or microfluidics.

The readout for the assay can be converted from a fluorescent readout as used in current microarray technology into a simple colorimetric format or one using physical detection methods such as changes in impedance, which can be read with minimal equipment. For example, this is achieved by utilising the Biotin currently used to attach fluorescent markers to DNA. Biotin has high affinity for avidin which can be used to attach enzymes such as peroxidase or other chromogenic substrates. This process will allow the quantity of cRNA binding to the target transcripts to be quantified using a chromogenic process rather than fluorescence. Simplified assays providing yes/no indications of disease status can then be developed by comparison of the colour intensity of the up- and down-regulated pools of transcripts with control colour standards. Similar approaches can enable detection of multiple gene signatures using physical methods such as changes in electrical impedance.

This aspect of the invention is likely to be particularly advantageous for use in remote or under-resourced settings or for rapid diagnosis in “near patient” tests. For example, places in Africa because the equipment required to read the chip is likely to be simpler.

Multiplex assay as employed herein refers to a type of assay that simultaneously measures several analytes (often dozens or more) in a single run/cycle of the assay. It is distinguished from procedures that measure one analyte at a time.

In one embodiment there is provided a bespoke gene chip for use in the method, in particular as described herein.

In one embodiment there is provided use of a known gene chip for use in the method described herein in particular to identify one or more gene signatures described herein.

In one embodiment there is provided a method of determining whether to administer an anti-bacterial agent to a subject, such as a subject suspected of having a bacterial infection for example a subject exhibiting symptoms of having a bacterial infection, by employing the method disclosed therein, and administering the anti-bacterial agent to the subject if the method indicates that the subject has a bacterial infection.

In one embodiment the subject exhibits clinical symptoms of having only a viral infection.

In another embodiment the subject exhibits clinical symptoms of having both a viral and a bacterial infection.

In one embodiment there is provided a method of treating a bacterial infection after diagnosis employing the method disclosed herein.

In one embodiment the bacterial infection is treated by administering one or more anti-bacterial agents to the subject.

In one embodiment the one or more anti-bacterial agents are selected from the group consisting of: erythromycin, clindamycin, gentamicin, tetracycline, meclocycline, sulfacetamide, benzoyl peroxide, azelaic acid, ceftobiprole, ceftaroline, dalbavancin, daptomycin, linezolid, mupirocin, oritavancin, tedizolid, telavancin, tigecycline, vancomycin, aminoglycosides, carbapenems, ceftazidime, cefepime, ceftobiprole, fluorquinolones, piperacillin/tazobactam, ticarcillin/clavulanic acid, linezolid, streptogramins, daptomycin, amikacin, kanamycin, neomycin, netilmicin, tobramycin, paromomycin, streptomycin, spectinomycin, geldanamycin, herbimycin, rifaximin, loracarbef, ertapenem, doripenem, imipenem/cilastatin, meropenem, cefadroxil, cefazolin, cefalotin, cefalexin, cefaclor, cefamandole, cefoxitin, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, ceftaroline fosamil, ceftobiprole, teicoplanin, telavancin, dalbavancin, oritavancin, clindamycin, lincomycin, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, troleandomycin, telithromycin, spiramycin, aztreonam, furazolidone, nitrofurantoin, linezolid, posizolid, radezolid, torezolid, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, methicillin, nafcillin, oxacillin, penicillin, penicillin G, penicillin V, piperacillin, temocillin, ticarcillin, amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, bacitracin, colistin, polymyxin B, ciprofloxacin, enoxacin, gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, trovafloxacin, grepafloxacin, sparfloxacin, temafloxacin, mafenide, sulfacetamide, sulfadiazine, silversulfadiazine, sulfadimethoxine, sulfamethizole, sulfamethoxazole, sulfanilimide, sulfasalazine,

sulfisoxazole, trimethoprim-sulfamethoxazole, sulfonamidochrysoidine, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, clofazimine, dapsone, capreomycin, cycloserine, ethambutol, ethionamide, isoniazid, pyrazinamide, rifampicin, rifabutin, rifapentine, arspenamine, chloramphenicol, fosfomycin, fusidic acid, metronidazole, mupirocin, platensimycin, quinupristin/dalfopristin, thiamphenicol, tinidazole and trimethoprim.

In one embodiment there is provided a method of determining whether to administer an anti-viral agent to a subject, such as a subject suspected of having a viral infection (for example a subject exhibiting symptoms of having a viral infection), by employing the method disclosed therein, and administering the anti-viral agent to the subject if the method indicates that the subject has a viral infection.

In one embodiment the subject exhibits clinical symptoms of having only a bacterial infection.

In another embodiment the subject exhibits clinical symptoms of having both a viral and a bacterial infection.

In one embodiment there is provided a method of treating a viral infection after diagnosis employing the method disclosed herein.

In one embodiment the viral infection is treated by administering one or more anti-viral agents to the subject.

In one embodiment the one or more anti-viral agents are selected from the group consisting of: amantadine, rimantadine, ritonavir, cobicistat, interferon alfa-2b/ribavirin, ombitasvir/paritaprevir/ritonavir, peginterferon alfa-2a, peginterferon alfa-2b, maraviroc, raltegravir, dolutegravir, elvitegravir, sofosbuvir, enfuvirtide, foscarnet, fomivirsen, zanamivir, oseltamivir, peramivir, nevirapine, etravirine, efavirenz, rilpivirine, delavirdine, nevirapine, daclatasvir, entacavir, lamivudine, adefovir, didanosine, tenofovir, abacavir, lamivudine, zidovudine, stavudine, emtricitabine, zalcitabine, telbivudine, didanosine, boceprevir, simeprevir, telaprevir, lopinavir, fosamprenavir, darunavir, ritonavir, tipranavir, atazanavir, nelfinavir, amprenavir, indinavir, saquinavir, ribavirin, valacyclovir, famciclovir, acyclovir, ganciclovir, valganciclovir and cidofovir.

In one embodiment there is provided a method of treating an inflammatory disease, such as JIA, HSP or SLE after diagnosis employing the method disclosed herein.

Gene signature, gene set, disease signature, diagnostic signature and gene profile are used interchangeably throughout and should be interpreted to mean gene signature.

In the context of this specification "comprising" is to be interpreted as "including".

Aspects of the invention comprising certain elements are also intended to extend to alternative embodiments "consisting" or "consisting essentially" of the relevant elements.

Where technically appropriate, embodiments of the invention may be combined.

Embodiments are described herein as comprising certain features/elements. The disclosure also extends to separate embodiments consisting or consisting essentially of said features/elements.

Technical references such as patents and applications are incorporated herein by reference.

Any embodiments specifically and explicitly recited herein may form the basis of a disclaimer either alone or in combination with one or more further embodiments.

EXAMPLES

Example 1

Method***Patient groups – Discovery and Validation groups***

The overall design of the study is shown in Figures 1 and 2. Patients were recruited prospectively as part of a UK National Institute of Health Research-supported study (NIHR ID 8209), the Immunopathology of Respiratory, Inflammatory and Infectious Disease Study (IRIS), which recruited children at three UK hospitals; patients were also recruited in Spain (GENDRES network, Santiago de Compostela), and USA (Rady Children's Hospital, San Diego). Inclusion criteria were fever (axillary temperature $\geq 38^{\circ}\text{C}$) and perceived illness of sufficient severity to warrant blood testing in children <17 years of age. Patients with co-morbidities likely to affect gene expression (bone marrow transplant, immunodeficiency, or immunosuppressive treatment) were excluded. Blood samples for RNA analysis were collected together with clinical blood tests at, or as close as possible to, presentation to hospital, irrespective of antibiotic use at the time of collection.

Additional validation groups

Additional validation groups (see also Table 2) included children with meningococcal sepsis,¹⁶ inflammatory diseases (Juvenile Idiopathic Arthritis and Henoch-Schönlein purpura) and published gene expression datasets which compared bacterial infection with viral infection,^{12,15,17} or inflammatory disease.¹⁸ Healthy children were recruited from out-patient departments. Data from healthy controls were not utilized in identification or validation of gene expression signatures, and were only used for interpretation of direction of gene regulation.

IRIS Discovery and IRIS Validation groups

Children were classified as Definite Bacterial if they had a clinical syndrome consistent with SBI (sepsis with shock or severe focal infection), and if pathogenic bacteria were detected at a usually sterile site (such as blood or CSF, excluding surface swabs, endotracheal secretions, or broncho-alveolar lavage samples); patients without sterile-site bacteria but with the other features listed above were categorized as Probable Bacterial. Children were classified as Definite Viral if they had a viral clinical syndrome, displayed no bacterial features, and matching virus was identified; patients without detected viruses but with clinical features of viral infection were classified as Probable Viral. In the absence of sterile site bacteria, children with inconclusive clinical features were classified as Unknown Bacterial or Viral. We used a CRP cut-off of above 60 mg/L for inclusion into the Probable Bacterial group, or exclusion from the Probable and Definite Viral groups; otherwise patients were categorized as Unknown. Inclusion in the Definite Bacterial group was irrespective of CRP. The indeterminate infection patients not selected for array were those with the most missing clinical data (Fig. 1B).

Healthy controls

In order to compare expression of identified biomarker genes with the healthy state and understand the direction of expression (up- or down-regulation), healthy children without intercurrent infection or recent immunization were recruited from the outpatient phlebotomy department (n=52). Data from healthy controls were not utilized in identification or validation of RNA expression signatures.

Meningococcal Validation cohort

We validated our expression signatures on children with meningococcal (gram-negative) infection (n=24), recruited to an earlier study at St Mary's Hospital, London, UK [29]. Following informed parental consent, and with approval of the hospital Local Research Ethics Committee (EC3263),

venous blood was collected on admission and within 24 hours of onset of symptoms from patients admitted to PICU at St Mary's hospital between December 2002 and May 2005 with suspected meningococcal sepsis, meningococcal meningitis or both. Group B meningococcus was detected in blood or CSF by culture or by bacterial DNA PCR amplification. Controls (used only for removal of array data batch effects) were healthy white adults recruited following informed consent [11 males, 10 females age median (IQR) 35.6 (30.8-44.5)].

Inflammatory Validation cohort

In order to establish if gene expression signatures could also distinguish children with bacterial infection from childhood inflammatory or vasculitic diseases, we used data from children with inflammatory diseases (Table 2). Patients were recruited at pediatric centers in the Netherlands and USA under approvals by the Research Ethics Committees of UCSD (Human Research Protection Program #140220), Amsterdam (NL41846.018.12 and NL34230.018.10). The inflammatory syndromes in the cohort were a) Henoch Schönlein Purpura (HSP) that was diagnosed in children presenting with palpable purpura, typically over the buttocks and extensor surfaces in association with abdominal pain, arthralgia or renal abnormalities (hematuria and proteinuria); and b) Juvenile Idiopathic arthritis (JIA) that was defined according to International League of Associations for Rheumatology [30]. Patients for the JIA cohort were recruited at initial presentation with early arthritis. They were not treated with DMARDs, corticosteroids or biologicals. Some patients used simple non-steroidal anti-inflammatory drugs.

Diagnostic process

All patients underwent routine diagnostic investigations as part of clinical care in each hospital's microbiology and virology laboratories, including blood count and differential, C-reactive protein (CRP), blood chemistry, blood, and urine cultures, and cerebrospinal fluid (CSF) analysis where indicated. Throat swabs were cultured for bacteria, and viral diagnostics were undertaken on nasopharyngeal aspirates using multiplex PCR for common respiratory viruses. Chest radiographs and other tests were undertaken as clinically indicated. Patients were assigned to diagnostic groups using predefined criteria (Fig. 1B). The Definite Bacterial group included only patients with culture confirmed infection, and the Definite Viral group included only patients with culture, PCR or immunofluorescent test-confirmed viral infection and no features of co-existing bacterial infection. Children in whom definitive diagnosis was not established (indeterminate infection) were categorized into Probable Bacterial, Unknown Bacterial or Viral, and Probable Viral groups based on level of clinical suspicion (Fig. 1B). Detection of virus did not prevent inclusion in the Definite, Probable Bacterial, or Unknown groups, as bacterial infection can occur in children co-infected with viruses.

Study conduct and oversight

Clinical data and samples were identified only by study number. Assignment of patients to clinical groups was made by consensus of two experienced clinicians independent of those managing the patient, after review of the investigation results and using previously agreed definitions (Fig. 1B). Statistical analysis was conducted after the gene expression data and clinical assignment databases had been locked.

Written, informed consent was obtained from parents or guardians at all sites using locally approved research ethics committee permissions (St Mary's Research Ethics Committee (REC 09/H0712/58

and EC3263); Ethical Committee of Clinical Investigation of Galicia (CEIC ref 2010/015); UCSD Human Research Protection Program #140220; and Academic Medical Centre, University of Amsterdam (NL41846.018.12 and NL34230.018.10).

Peripheral blood gene expression by microarray

5 Whole blood (2.5ml) was collected at the time of recruitment into PAXgene blood RNA tubes (PreAnalytiX, Germany), incubated for two hours, frozen at -20°C within six hours of collection, before storage at -80°C. Total RNA was extracted using PAXgene blood RNA kits (PreAnalytiX, Germany) according to the manufacturer's instructions. The integrity and yield of the total RNA was assessed using an Agilent 2100 Bioanalyser and a NanoDrop 1000 spectrophotometer. After
10 quantification and quality control, biotin-labeled cRNA was prepared using Illumina TotalPrep RNA Amplification kits (Applied Biosystems) from 500ng RNA. Labeled cRNA was hybridized overnight to Human HT12-V4 Expression BeadChip arrays (Illumina) [Discovery cohort, Inflammatory Validation cohort] or Human HT12-V3 Expression BeadChip arrays (Illumina) [IRIS validation cohort] or Human Ref-8 V3 Beadchip (Meningococcal validation cohort). After washing, blocking, and
15 staining, the arrays were scanned using an Illumina BeadArray Reader according to the manufacturer's instructions. Using Genome Studio software, the microarray images were inspected for artifacts and QC parameters were assessed. No arrays were excluded at this stage.

Statistical Analysis

Microarray pre-processing

20 Expression Data was analyzed using 'R' *Language and Environment for Statistical Computing (R) 3.1.2* [31]. Expression values were transformed to a logarithmic scale (base 2). Mean raw intensity values for each probe were corrected for local background intensities and robust spline normalization [32] (combining quantile normalization and spline interpolation) was applied. Principal Component Analysis (PCA) was used as part of the quality control process. PCA is an approach that allowed us to
25 summarize our data and reduce the dimensionality (240 arrays x 48,000 probes, down to 240 arrays x no of principal components) in order to explore variance in the expression level [33]. Transcript expression profiles of all samples in the discovery dataset clustered together on PCA; regardless of the diagnostic group (Fig. 6). All the samples were within the confidence ellipse (level: 0.999). The arrays in the discovery dataset that correspond to patients with definite diagnosis were divided into
30 80%-20% for the identification and validation of expression signatures, resulting in a balanced training set ($n_{\text{adenovirus}}=18$, $n_{\text{flu}}=18$, $n_{\text{RSV}}=22$, $n_{\text{other viral}}=15$, $n_{\text{bacterial gram-negative}}=20$, $n_{\text{bacterial gram-positive}}=22$) and test set ($n_{\text{adenovirus}}=5$, $n_{\text{flu}}=5$, $n_{\text{RSV}}=5$, $n_{\text{other viral}}=4$, $n_{\text{bacterial gram-negative}}=5$, $n_{\text{bacterial gram-positive}}=5$).

Identification of expression signatures

For the discovery dataset, we used transcripts that were measured on both V3 and V4 Illumina
35 BeadChips (the intersection array IDs). Using the training set, we identified the transcripts that were significantly differentially expressed between the definite viral and definite bacterial groups with $|\log_2 \text{FC}| > 1$ and adjusted P-value < 0.05 , using a linear model for expression, conditional on recruitment site. These thresholds were chosen to ensure that differential expression for selected variables could be distinguished using the resolution of other validation techniques (i.e. qPCR). The
40 transcripts that fulfilled the above criteria were taken forward to variable selection with elastic net, using glmnet [34] package in R. The parameters of elastic net, which control the size of the selected model, were optimized via ten-fold cross-validation (CV).

In order to identify a smaller signature, we applied a novel in-house forward selection algorithm to discover a transcript signature, Forward Selection – Partial Least Squares (FS-PLS) which was then implemented as a Disease Risk Score (DRS) in order to translate the minimal multi-transcript signature into a value that could be assigned to each individual to form the basis of a simple diagnostic test. The DRS is calculated by adding the total intensity of the up-regulated transcripts (relative to comparator group) and subtracting the total intensity of the down-regulated transcripts (relative to comparator group) in the signature [11, 20]. The disease risk score for individual i is:

$$\text{Disease Risk Score}^i = \sum_{k=0}^n \text{expr. value}_k^i - \sum_{l=0}^m \text{expr. value}_l^i \quad (1)$$

where:

n the number of up-regulated probes in the signature in disease of interest (bacterial infection) compared to comparator group (viral infection) and

m the number of down-regulated probes in the signature in disease of interest (bacterial infection) compared to comparator group (viral infection).

In order to discover gene expression signatures using FS-PLS, the first iteration of the algorithm considers the expression levels of all transcripts (N) and initially fits N univariate regression models. The regression coefficient for each model is estimated using the Maximum Likelihood Estimation (MLE) function, and the goodness of fit is assessed by means of a t-test. The variable with the highest MLE and smallest p-value is selected first (SV1). Before selecting which of the $N-1$ remaining variables to use next, the algorithm projects the variation explained by SV1 using Singular Value Decomposition. The algorithm iteratively fits up to $N-1$ models, at each step projecting the variation corresponding to the already selected variables, and selecting new variables based on the residual variation. This process terminates when the MLE p-value exceeds a pre-defined threshold. The final model includes regression coefficients for all selected variables.

The performance of both the signatures was assessed on the 20% test and the IRIS validation dataset. The probable viral and bacterial groups as well as the unknown bacterial or viral infection group from the discovery cohort were assessed with the 20% test dataset. The thresholds for the classification throughout were calculated using the pROC package in R [35], employing the Youden's J statistic [36]. The optimal threshold was determined by the point in the ROC curve that maximizes the distance to the identity line (maximum of (sensitivities + specificities)).

In the boxplots, boxes show median with 25th and 75th quartiles and whiskers show “range” (defined by boxplot function in R). With a “range” value set at 1, the whiskers extend no more than 1 times the interquartile range. For the 2-transcript signature, the DRS was calculated by subtracting the $\log_2$ transformed expression value of *IFI44L* from the $\log_2$ transformed *FAM89A* expression value for every patient. The range of DRS in the population can be between: [the minimum *FAM89A* value – the maximum *IFI44L*, the maximum *FAM89A* value – the minimum *IFI44L* value].

The signatures identified in the discovery group were then externally validated on our previously published validation group [13] additional patient groups with meningococcal disease and inflammatory diseases, and three published pediatric data sets (Fig.2).

Analysis of IRIS validation dataset

The IRIS validation dataset (analysed using HT-12-V3 Illumina BeadChip arrays) was pre-processed and analysed separately to the discovery dataset, using the same approach.

Analysis of additional validation datasets

To assess the performance of the signature in gram-negative bacterial infection, the IRIS validation dataset was merged with a dataset containing pediatric meningococcal infection and healthy controls. As the meningococcal and IRIS validation cohorts had been run on different versions of the Illumina chip, the data were merged for analysis using the ComBat method [37] to remove unwanted batch effects using transcripts common to the 2 platforms. The healthy controls in the IRIS validation set (Illumina HT12-V3), and the healthy controls in the meningococcal validation set (Illumina Ref-8) were used for the adjustment. One binary covariate was passed to ComBat which assigned samples to two groups - healthy, and disease. (Fig. 11)

The inflammatory validation dataset contained JIA and HSP patients run on Illumina HT12-V4 arrays. These arrays were processed and normalized alongside the Discovery arrays, and the discriminatory power of the 2-transcript signature was applied without further pre-processing of array data.

To further validate the performance of the disease risk score based on the 2-transcript signature, we used publicly available microarray expression datasets with bacterial infections and comparator groups run simultaneously on the same platform to avoid the introduction of batch effects, as follows:

1. GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 [15] (accession series GSE6269) dataset. The dataset consists of 22 pediatric cases, 10 viral and 12 bacterial; 7 children were diagnosed with Influenza A, 3 with Influenza B, 6 with *S. pneumoniae* and 6 with *S. aureus* infection. Gene identities for the two genes in our signature from the Illumina arrays were mapped to the Affymetrix dataset and "204439_at" for *IFI44L* and "226448_at" for *FAM89A* transcript ids were used. Despite differences in experimental design - the GSE6269 gene expression dataset was acquired from peripheral blood mononuclear cells using a non-Illumina platform, the 2-transcript signature DRS had a sensitivity of 100% (95% CI, 100 to 100) and a specificity of 90% (95% CI, 70 to 100), misclassifying only one viral patient with Influenza A (patient id: GSM173316). The AUC was 96% (95% CI, 85 to 100) (Figure 12).
2. GSE40396 dataset. This includes 30 febrile children with viral infection (8 with adenovirus, 6 with enterovirus and 8 with HHV6) and 8 with bacterial infection (MRSA, MSSA, salmonella and *E.coli*) [12]. As the arrays used were Illumina HT12-V4, the same probe ids for *IFI44L* and *FAM89A* were identified. The 2-transcript signature had a sensitivity of 100% (95% CI, 100 to 100) and a specificity of 77.3% (95% CI, 59.1 to 95.5) and an AUC of 89.2% (95% CI, 75.6 to 98.3).
3. GSE22098 dataset. This includes 48 children (aged <17 years) with bacterial infection (*S. pneumoniae* and *S. aureus*) and 31 children with systemic lupus erythematosus [18], run on Illumina Beadchip HT12-V3 arrays. The same probe IDs for the two-transcript signature were available on both HT12-V3 and V4 arrays, and were applied to the data. The 2-transcript signature had a sensitivity for detection of bacterial infection of 93.5% (95% CI, 83.9 to 100) and a specificity of 96.1% (95% CI, 96.9 to 100) and an AUC of 96.6% (95% CI, 91.9 to 100).
4. GSE60244 dataset. This dataset includes patients with bacterial lower respiratory tract infection (LRTI) n=22 and viral LRTI n=71 run on Illumina Beadchip HT12-V4 arrays. As the arrays used were Illumina HT12-V4, the same probe ids for *IFI44L* and *FAM89A* were identified. The 2-transcript signature had a sensitivity for detection of bacterial infection of

90.1 (95% CI, 77.3 to 100) and a specificity of 80.3 (95% CI, 70.4 to 88.7) and an AUC of 89.8 (95% CI, 83.4-95.5).

Results

240 patients were recruited to the discovery group, including a Definite Bacterial group with 52 patients and Definite Viral group with 92 patients. These were subdivided into 80% and 20% - forming a training set and test set respectively (Figs. 1A, 2). The test set (20%) also included 96 children whose infection was not definitively diagnosed (indeterminate) (Figs. 1A, 2). The validation groups comprised 130 children previously recruited[13] (IRIS validation – with 23 Definite Bacterial, 28 Definite Viral patients and 79 patients with indeterminate infection) and 72 other children (additional validation – with 24 meningococcal infection, 30 juvenile idiopathic arthritis, and 18 patients with Henoch-Schönlein purpura) (Figs. 1A, 2). The numbers in each diagnostic category in the discovery, IRIS validation and additional validation groups and their clinical features are shown in Table 1 and Table 2. Details of the types of infection are shown in Table 3. Gene expression profiles of children in the discovery group clustered together on Principal Component Analysis (Fig. 6).

Identification of minimal transcript signatures

Of the 8565 transcripts differentially expressed between bacterial and viral infections, we identified 285 transcripts as potential biomarkers after applying the screening filters based on log fold change and statistical significance (see methods). Variable selection using elastic net identified 38 of these transcripts (Table 4) as best discriminators of bacterial and viral infection in the discovery test set with sensitivity of 100% (95% CI, 100-100) and specificity of 95% (95% CI, 84 -100) (Table 5). In the IRIS validation group, this signature had an area under the curve (AUC) of 98% (95%CI, 94-100), sensitivity of 100% (95% CI, 100-100), and specificity of 86% (95% CI, 71-96) for distinguishing bacterial from viral infection (Table 5, Figs. 7, 8). The putative function of the 38 transcripts in our signature, as defined by Gene Ontology is shown in Table 6.

After using the novel forward selection process (FS-PLS) to remove highly correlated transcripts, a two-transcript gene signature which distinguished bacterial from viral infections: interferon-induced protein 44-like (*IFI44L*, RefSeq ID: NM_006820.1), and family with sequence similarity 89, member A (*FAM89A*, RefSeq ID: NM_198552.1). Both transcripts were also included in the larger 38 transcript signature.

Implementation of a simplified disease risk score

The expression data of both genes in the signature was combined into a single Disease Risk Score for each patient, using the reported DRS method which simplifies application of multi transcript signatures as a diagnostic test. [20] The sensitivity (95% CI) of the DRS in the training, test and validation sets respectively was: 86% (74-95), 90% (70-100), and 100% (100-100) (Fig. 3A-D, Fig. 9 and Table 5). Expression of *IFI44L* was increased in viral patients and *FAM89A* was increased in bacterial patients relative to healthy children (Table 4). The summary of diagnostic test accuracy including STARD flow diagrams are shown in Fig. 10.

For additional validation the 2-transcript signature was applied to patients with meningococcal disease (Fig. 11), inflammatory diseases (Juvenile Idiopathic arthritis and Henoch-Schönlein purpura), and published datasets for children and adults with bacterial or viral infection, and inflammatory disease (pediatric SLE).[12, 15, 17, 18] The 2-transcript signature distinguished

bacterial infection from viral infection and inflammatory disease in all these datasets with AUC ranging from 89% to 98% (Table 7 and Figure 12-13).

Effect of viral and bacterial co-infection

The effect of viral co-infection on the signatures was investigated (Table 1). 30 of 47 (64%) of the definite bacterial infection group who were tested had a virus isolated from nasopharyngeal samples. There was no significant difference in DRS score between those with and without viral co-infection.

DRS score in patients with indeterminate infection status

The classification performance of the DRS was investigated in patients with indeterminate viral or bacterial infection status. Patients were separated into those with clinical features strongly suggestive of bacterial infection (Probable Bacterial), those with features consistent with either bacterial or viral infection (Unknown), and those with clinical features and results suggestive of viral infection (Probable Viral) as in Fig. 1B. The Probable Bacterial and Unknown groups included patients with DRS values that indicated viral infection, despite having clinical features that justified initiation of antibiotics by the clinical team. The median DRS showed a gradient of assignment that followed the degree of certainty in the clinical diagnosis, although many of the indeterminate group DRS values overlapped with those of Definite Bacterial and Definite Viral groups (Fig. 4A, 4B).

For patients in the indeterminate groups, we compared DRS assignment as 'viral' or 'bacterial' to clinical variables (Table 8). CRP is widely used to aid distinction of bacterial from viral infection and was included in the categorization of Definite Viral, Probable Bacterial, and Probable Viral infection in this study; patients assigned as bacterial by DRS had higher CRP levels than those assigned as viral infection (median [IQR]: 101 [48-192] and 71 [27-120] mg/l; $p=0.015$ respectively). They also had increased incidence of shock ($p=0.006$), requirement for ventilator support ($p=0.048$) and intensive care admission ($p=0.066$). There was a non-significant increase in white cell and neutrophil counts in patients assigned by DRS as bacterial or viral respectively: (median [IQR] 14.1 [8.3-19.4] and 11.1 [7.3-16.0] for white cells; 8.7 [5.0-13.8] and 6.8 [3.5-11.4] for neutrophils), ($p=0.079$ and 0.114 respectively).

Antibiotic use

The number of children treated with antibiotics was compared with DRS prediction of bacterial or viral infection. There were high rates of antibiotic use in all groups, including >90% in the Unknown group. The high rate of antibiotic use in the indeterminate groups contrasted with the low numbers predicted to have bacterial infection by both DRS and clinical assignment (Fig. 5).

Illness severity and duration

The study recruited a high proportion of seriously ill patients needing intensive care, thus raising concern that selection bias might have influenced performance of the signature. To exclude bias based on severity or duration of illness, performance of the DRS was evaluated after stratification of patients into those with milder illness or severe illness requiring intensive care, and by duration of reported illness before presentation. The DRS distinguished bacterial from viral infection in both severe and milder groups (Fig. 14), and irrespective of day of illness (Fig. 15).

Discussion

We have identified a host whole blood RNA transcriptomic signature that distinguishes bacterial from viral infection with only two transcripts. The signature also distinguishes bacterial infection from childhood inflammatory diseases, SLE, JIA and HSP and discriminates bacterial from viral

infection in published adult studies [12, 15, 17, 18]. The design of our study with recruitment of febrile patients to a discovery set and then evaluation of the diagnostic signature in a separate validation set and in multiple additional datasets, recruited in different centres and analysed on various microarray platforms, ensures that our findings are robust. The results extend previous gene expression studies in single infections that suggest that bacterial and viral infections have different signatures, and that this approach is superior to non-specific markers such as CRP or procalcitonin alone [12, 13, 17, 21].

The transcripts identified in the larger 38-transcript elastic net gene signature comprise a combination of transcripts up-regulated by viruses or by bacteria. The two transcripts *IFI44L* and *FAM89A* in the smaller 2 transcript signature show reciprocal expression in viral and bacterial infection, and are differentially expressed when bacterial or viral patients were compared to healthy controls[20].

An obstacle in the development of improved tests to distinguish bacterial from viral infection is the lack of a gold standard. Some studies include patients with “clinically diagnosed bacterial infection” who have features of bacterial infection but cultures remain negative. Negative cultures may reflect prior antibiotic use, low numbers of bacteria, or inaccessible sites of infection. If patients with indeterminate status are included in biomarker discovery, there is a risk that the identified biomarker will not be specific for “true” infection. This study adopted the rigorous approach of identifying the signature in culture-confirmed cases, and using the signature to explore likely proportions of “true” infection in the indeterminate groups.

The proportion of children predicted by DRS signature to have bacterial infection follows the level of clinical suspicion (greater in Probable Bacterial and less in the Probable Viral groups), thus supporting the hypothesis that the signatures may be an indication of the true proportion of bacterial infection in each group. Furthermore, a higher proportion of patients in the indeterminate group, assigned as bacterial by the signature (Probable and Unknown groups) had clinical features normally associated with severe bacterial infection, including increased need for intensive care, and higher neutrophil counts, and CRP, suggesting that the signature may be providing additional clues to the presence of bacterial infection.

The decision to initiate antibiotics in febrile children is largely driven by fear of missing bacterial infection. A test that correctly distinguishes children with bacterial infection from those with viral infections would reduce inappropriate antibiotic prescription and investigation. The DRS predicts that many children who were prescribed antibiotics did not have a bacterial illness (see Fig. 5). If the score reflects the true likelihood of bacterial infection, its implementation could reduce unnecessary investigation, hospitalization, and treatment with antibiotics. Confirmation that the DRS provides an accurate estimate of bacterial infection in the large group of patients with negative cultures, for whom there is no gold standard, can only be achieved in prospective clinical trials. Careful consideration will be needed to design an ethically acceptable and safe trial in which observation without antibiotic administration is undertaken for febrile children predicted by DRS to be at low risk of bacterial infection.

In comparison with the high frequency of common viral infections in febrile children presenting to healthcare, inflammatory and vasculitic illness are very rare.[24-27] However, children presenting with inflammatory or vasculitic conditions commonly undergo extensive investigation to exclude

bacterial infection and treatment with antibiotics before the correct diagnosis is made. Although children with inflammatory conditions were not included in the discovery process, the 2-transcript signature was able to distinguish bacterial infection from SLE, JIA and HSP.

A major challenge in using transcriptomic signatures as diagnostic tools is the translation of multi-transcript signatures into clinical tests suitable for use in hospital laboratories or at the bedside. The DRS gene signature, distinguishing viral from bacterial infections with only two transcripts, has potential to be translated into a clinically applicable test using current technology such as real-time PCR.[28] Furthermore, new methods for rapid detection of nucleic acids including nanoparticles, and electrical impedance have potential for low-cost direct and rapid analysis of multi-transcript signatures. This may be particularly advantageous for the implementation of the DRS based test in resource poor settings such as in remote villages.

In summary, our work provides proof of principle that as few as two gene transcripts can discriminate between bacterial and viral infection in children with a high degree of sensitivity and specificity. A rapid test based on our signatures could potentially reduce unnecessary investigation, admission, and antibiotic prescription.

Example 2

Herberg and colleagues (49), in a preliminary, cross-sectional study of 370 febrile children (aged <17 years) in Europe and the United States, reported that children with bacterial infection may be characterized by the difference in blood RNA expression values of 2 genes. In a recent study, Mahajan and colleagues [50] reported a 66-transcript blood RNA signature that distinguished bacterial from viral infection in 279 febrile infants younger than 60 days. To provide further validation of the 2-transcript signature (*IFI44L* and *FAM89A*) and to evaluate its performance in an infant population, the 2-transcript signature was further applied to the RNA expression data of Mahajan et al.

Methods

Institutional review board approval was obtained from all 22 sites in the Pediatric Emergency Care Applied Research Network included in the study by Mahajan et al. Parents or guardians provided written informed consent. The RNA expression data of Mahajan et al were downloaded from the Gene Expression Omnibus database accession GSE64456 (51), obtained from a convenience sample of febrile neonates and infants less than 60 days who were recruited from 22 US emergency departments between 2008 and 2010. 89 infants had culture-positive bacterial infections (32 with bacteremia and 57 with urinary tract infection) and 190 had negative bacterial cultures (111 with proven viral infection, 38 not tested for viruses, and 41 with negative test results). After logarithmic transformation, robust spline normalization and quality control using the lumi Bioconductor package in R (R Foundation), version 3.3.1, the expression values for the 2-signature transcripts *IFI44L* (RefSeq ID NO: NM_006820.1) and *FAM89A* (RefSeq ID NO: NM_198552.1) were extracted for each patient. These values were combined into a single disease risk score (DRS) as described in Kaforou et al [20], by subtracting the intensity of the *IFI44L* transcript from the intensity of the *FAM89A* transcript. We evaluated the predictive accuracy of the DRS first in patients with microbiologically confirmed diagnoses, and then in patients without definite clinical diagnosis. Using the pROC package in R [35], we calculated the area under the characteristic curve (AUC), sensitivity, specificity, and their 95% CIs under the negative binomial distribution.

Results

When the 2-transcript DRS signature was applied to infants with definite bacterial diagnoses (n=89) and proven viral infections (n=111), sensitivity was 88.8% (95% CI, 80.3%-94.5%), specificity was 93.7% (95% CI, 87.4%-97.4%) and AUC was 95.7% (95% CI, 92.6%-98.3%) See Figure 16. The signature distinguished patients with a definite bacterial diagnosis from those with negative results for viruses (n=41) or no viral tests performed (n=38) with specificities of 48.8% (95% CI, 32.8%-64.9%) and 78.9% (95% CI, 62.7%-90.5%), whereas the sensitivities remained unchanged. The AUC was 80.5% (95% CI, 72.4%-87.5%) for those with negative results and 90.9% (95% CI, 84.8%-95.9%) for those with no viral test.

Discussion

The studies by Herberg et al and Mahajan et al reported sensitivities of 100% (95% CI, 85%-100%) and 87% (95% CI, 73%-95%), respectively, and specificities of 96.4% (95% CI, 89.3%-100%) and 89% (95% CI, 81%-93%), respectively, for the discrimination of bacterial from viral and non-bacterial infections. In this study, the 2-transcript RNA signature, which was originally identified and validated in children with a mean age of 19 months, also had high sensitivity and specificity in the specific population of infants younger than 60 days.

Accordingly, the 2-gene DRS has the potential to translate into a simple bedside diagnostic test for infants.

Example 3

Paired-end and stranded RNA-Seq of RNA extracted from the whole blood of 97 patients (see Figure 17A) was performed. The data has been analysed and some of the results are shown in Figures 17B & C. The dataset included 66 bacterial (culture confirmed) and 31 viral patients. Raw reads were trimmed using Trimmomatic, aligned to the Ensembl reference genome 38 using the STAR aligner and Samtools was used for the manipulation of alignments. Expression quantification was performed using FeatureCounts.

The counts for *IFI44L* and *FAM89A* were employed to calculate a Disease Risk Score for each one of the patients in the dataset. The AUC was 96.8% and the CI 95% (93.4-99.1%). As the counts are more comparable to the measures which would be obtained as part of a point-of-care test vs microarray expression values, the validation of the 2-gene signature using RNA-seq highlights even more its point-of-care potential.

Table 1 Demographic and clinical features of the study groups

	Discovery			IRIS Validation		
	Definite Bacterial	Definite Viral	Indeterminate ^a	Definite Bacterial	Definite Viral	Indeterminate ^a
Number of patients	52	92	96	23	28	79
Age - mo. median (IQR)	22 (9-46)	14 (2-39)	27 (7-71)	22 (13-52)	18 (7-48)	15 (2-44)
Male, No. (%)	22 (42%)	65 (71%)	62 (65%)	10 (43%)	17 (61%)	47 (59%)
White ethnicity ^b - no. (%)	35/48 (73%)	46/87 (53%)	47/85 (55%)	12/22 (55%)	14/27 (51%)	42/71 (59%)
Days from symptoms ^c - median (IQR)	5 (2-8.8)	4.5 (3.0-6.0)	5 (4.8-8)	4 (2.5-8)	3.5 (2.8-5.3)	4 (3-7)
Intensive care - no. (%)	36 (69%)	32 (35%)	57 (59%)	13 (57%)	7 (23%)	42 (53%)
Deaths - no.	10	0	2	1	1	8
CRP ^d (mg/dl) - median (IQR)	17.6 (9.8-27.5)	1.6 (0.6-2.7)	10.2 (4.7-17.6)	21.7 (16.8-28.5)	0.7 (0.1-2.0)	6.7 (2.5-12.8)
Neutrophil %: median (IQR)	75 (49-85)	50 (36-63)	63 (46-79)	82 (71-88)	53 (41-69)	64 (43-82)
Lymphocytes %: median (IQR)	19 (10-36)	34 (20-44)	22 (15-42)	15 (8-23)	32 (26-48)	30 (14-42)
Monocyte %: median (IQR)	5 (3-8)	10 (4-14)	6 (2-12)	3 (0-7)	7 (5-10)	5 (2-8)
Main clinical syndrome						
Bone, joint, soft tissue infection	5	0	0	1	0	0
Fever without source/sepsis	21	7	9	5	2	6

Gastroenteritis	0	0	0	1	0	1	2
Meningitis/encephalitis	14	3	3	5	1	1	1
Respiratory (upper + lower)	10	81	83	11	23	68	
Other	2	1	0	1	1	2	
Virus detected ^e (%)	22/34 (65%)	92/92 (100%)	62/87 (71%)	8/13 (62%)	28/28 (100%)	52/77 (68%)	
IQR= interquartile range							

^a The indeterminate group in the discovery set comprised 42 Probable Bacterial, 49 Unknown bacterial or viral, and 5 Probable Viral patients. The intermediate group in the validation cohort comprised 17 Probable Bacterial, 55 Unknown bacterial or viral, and 7 Probable Viral patients respectively.

^b self-reported ethnicity, where stated,

^c until sampling,

^d maximum value of CRP in illness is reported,

^e Denominator denotes number of patients with viral investigations.

Table 2. Demographic and clinical features of the validation groups.

	Meningococcal Disease^a	Juvenile Idiopathic Arthritis^b	Henoch-Schönlein purpura^c
Number of patients	24	30	18
Age - mo. median (IQR)	23 (17-35)	163 (124-187)	56 (43-81)
Male, No. (%)	16 (66%)	11 (37%)	9 (50%)
White ethnicity - no. (%)	24/24 (100%)	27/30 (90%)	4/18 (22%)
Days from symptoms - median (IQR)	1(1-1)	n/a	3.5 (2-6)
Intensive care, No. (%)	24 (100%)	0	0
Deaths, No. (%)	3 (12.5%)	0	0
CRP (mg/dl) - median (IQR)	6.8 (3.4-10)	0.1 (0.0-0.2)	2.2 (0.8-2.4)
Neutrophil %: median (IQR)	71 (56-83)	51 (45-57)	60 (45-68)
Lymphocyte %: median (IQR)	23 (12-53)	37 (33-45)	26 (16-34)
Monocyte %: median (IQR)	ND	7 (6-8)	7 (5-8)

^a sample size for data fields: % neutrophil n=20, % lymphocyte n=12, CRP n=22.

^b sample size for JIA (juvenile idiopathic arthritis) disease categories: enthesitis-related arthritis n=6, extended oligoarthritis n=4, persistent oligoarthritis n=4, polyarthritis rheumatoid factor (RF)-negative n=12, polyarthritis RF-positive n=1, psoriatic n=3. Sample size for data fields: % neutrophil n=27, % lymphocyte n=27, % monocyte n=27

^c HSP (Henoch-Schönlein purpura). Sample size for data fields: % neutrophil n=15, % monocyte n=15, CRP n=8

Table 3. Viral and Bacterial causative pathogens in patients in the Definite Bacterial and Viral groups in the discovery and IRIS validation cohorts.

	Definite Viral		Definite Bacterial	
	Discovery (n)	Validation (n)	Discovery (n)	Validation (n)
Viral causative pathogen				
Adenovirus	23	2		
Influenza A or B	23	13		
RSV	27	10		
Other	19	3		
Bacterial causative pathogen				
<i>S.pneumoniae</i>			10	15
<i>S.aureus</i>			2	2
<i>S.pyogenes</i>			10	5
Group B streptococcus			4	
<i>E.coli</i>			2	
<i>N.meningitidis</i>			17	24
<i>Enterococcus</i>			1	
<i>Kingella</i>			1	
<i>H.influenzae</i>			1	
<i>Pseudomonas</i> spp			3	
<i>Stenotrophomonas</i>			1	
<i>Klebsiella</i>				1
Total number of patients	92	28	52	47

Table 4. 38-transcript signature for distinguishing bacterial from viral infection.

Array ID	Elastic net co-efficient	Transcript ID	Official Symbol (HGNC)	Definition	Definite Bacterial vs. Definite Viral		Definite Bacterial vs Healthy Control		Definite Viral vs Healthy Control	
					log ₂ FC	q-value ^a	log ₂ FC	q-value ^a	log ₂ FC	q-value ^a
3990170	-0.18	ILMN_17548	<i>IFI27</i>	Homo sapiens interferon, alpha-inducible protein 27, transcript variant 2, mRNA.	-4.32	4.78E-21	1.08	7.06E-02	5.40	3.15E-23
3870338 *	-0.02	ILMN_9752	<i>IFI44L</i>	Homo sapiens interferon-induced protein 44-like, mRNA.	-3.79	1.36E-22	-1.11	1.98E-02	2.68	4.45E-10
2000148	-0.06	ILMN_1751	<i>IFIT1</i>	Homo sapiens interferon-induced protein with tetratricopeptide repeats 1, transcript variant 2, mRNA.	-3.49	2.90E-20	-1.15	1.48E-02	2.35	3.89E-08
3360343	-0.03	ILMN_37168	<i>RSAD2</i>	Homo sapiens radical S-adenosyl methionine domain containing 2, mRNA.	-3.28	5.14E-19	-0.75	1.48E-01	2.53	2.11E-09
6510170	-0.04	ILMN_22925	<i>IFIT3</i>	Homo sapiens interferon-induced protein with tetratricopeptide repeats 3, mRNA.	-2.66	2.47E-16	-0.90	3.77E-02	1.77	3.25E-06
520408	-0.04	ILMN_1944	<i>IFIT3</i>	Homo sapiens interferon-induced protein with tetratricopeptide repeats 3, mRNA.	-2.56	1.20E-16	-0.94	1.90E-02	1.62	7.09E-06
1440615	-0.05	ILMN_27303	<i>OTOF</i>	Homo sapiens otoferlin, transcript variant 4, mRNA.	-2.53	1.73E-14	0.08	9.22E-01	2.61	4.01E-11
2600747	-0.07	ILMN_28123	<i>IFIT2</i>	Homo sapiens interferon-induced protein with tetratricopeptide repeats 2, mRNA.	-2.40	7.83E-17	-1.15	1.22E-03	1.25	2.33E-04

Array ID	Elastic net co-efficient	Transcript ID	Official Symbol (HGNC)	Definition	Definite Bacterial vs. Definite Viral		Definite Bacterial vs Healthy Control		Definite Viral vs Healthy Control	
					log ₂ FC	q-value ^a	log ₂ FC	q-value ^a	log ₂ FC	q-value ^a
5700725	-0.05	ILMN_27754	<i>EPSTI1</i>	Homo sapiens epithelial stromal interaction 1 (breast), transcript variant 2, mRNA.	-2.23	1.90E-20	-0.55	8.77E-02	1.69	5.76E-10
2030309	-0.05	ILMN_15074	<i>SERPING1</i>	Homo sapiens serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, transcript variant 2, mRNA.	-2.19	4.14E-12	-0.18	7.94E-01	2.01	9.82E-08
1090390	-0.04	ILMN_2717	<i>OAS1</i>	Homo sapiens 2',5'-oligoadenylate synthetase 1, 40/46kDa, transcript variant 3, mRNA.	-2.13	2.10E-18	-0.27	5.13E-01	1.86	5.60E-11
5090215	-0.17	ILMN_13978	<i>IFI6</i>	Homo sapiens interferon, alpha-inducible protein 6, transcript variant 3, mRNA.	-1.55	1.23E-18	-0.41	8.55E-02	1.14	1.53E-08
620544	-0.13	ILMN_5312	<i>HLA-DRB6</i>	Homo sapiens major histocompatibility complex, class II, DR beta 6 (pseudogene), non-coding RNA.	-1.42	8.94E-05	-1.93	2.02E-05	-0.51	4.40E-01
6980192	-0.02	ILMN_19775	<i>HBZ</i>	Homo sapiens hemoglobin, zeta, mRNA.	-1.33	2.85E-03	-0.43	5.97E-01	0.90	1.69E-01
1030100	-0.22	ILMN_89157	<i>HS.386275</i>	cl02h05.z1 Hembase; Erythroid Precursor Cells (LCB:cl library) Homo sapiens cDNA clone cl02h05 5, mRNA sequence	-1.31	2.84E-14	-0.42	8.24E-02	0.89	1.19E-05
2120079	-0.11	ILMN_168435	<i>EIF2AK2</i>	Homo sapiens eukaryotic translation initiation factor 2-alpha kinase 2, mRNA.	-1.24	1.25E-12	-0.08	8.48E-01	1.16	2.55E-08

Array ID	Elastic net co-efficient	Transcript ID	Official Symbol (HGNC)	Definition	Definite Bacterial vs. Definite Viral		Definite Bacterial vs Healthy Control		Definite Viral vs Healthy Control	
					log ₂ FC	q-value ^a	log ₂ FC	q-value ^a	log ₂ FC	q-value ^a
3780452	-0.01	ILMN_5646	<i>IFIT1L</i>	Homo sapiens interferon-induced protein with tetratricopeptide repeats 1-like, mRNA.	-1.18	5.13E-03	0.29	7.22E-01	1.47	3.89E-03
3360615	-0.04	ILMN_18288	<i>FCER1A</i>	Homo sapiens Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide, mRNA.	-1.13	6.50E-07	-2.80	2.28E-19	-1.66	2.24E-09
150315	-0.18	ILMN_9078	<i>C21ORF7</i>	Homo sapiens chromosome 21 open reading frame 7, mRNA.	-1.12	3.53E-11	-1.11	1.18E-07	0.01	9.86E-01
6940086	-0.02	ILMN_21264	<i>GYPE</i>	Homo sapiens glycoporphin E, transcript variant 1, mRNA.	-1.11	2.37E-03	0.33	6.31E-01	1.44	1.06E-03
3780187	-0.06	ILMN_27651	<i>GYPB</i>	Homo sapiens glycoporphin B (MNS blood group), mRNA.	-1.09	3.03E-03	0.46	4.56E-01	1.55	3.76E-04
4480730	-0.12	ILMN_2819	<i>HBM</i>	Homo sapiens hemoglobin, mu, mRNA.	-1.02	1.03E-04	0.08	8.98E-01	1.10	6.73E-04
4150600	-0.19	ILMN_14704	<i>EIF1AY</i>	Homo sapiens eukaryotic translation initiation factor 1A, Y-linked, mRNA.	-1.00	1.61E-02	0.24	7.73E-01	1.24	1.43E-02
1010546	-0.02	ILMN_43805	<i>LOC649143</i>	PREDICTED: Homo sapiens similar to HLA class II histocompatibility antigen, DRB1-9 beta chain precursor (MHC class I antigen DRB1*9) (DR-9) (DR9), transcript variant 2, mRNA.	-0.95	2.37E-04	-1.33	3.83E-05	-0.37	4.16E-01

Array ID	Elastic net co-efficient	Transcript ID	Official Symbol (HGNC)	Definition	Definite Bacterial vs. Definite Viral		Definite Bacterial vs Healthy Control		Definite Viral vs Healthy Control	
					log ₂ FC	q-value ^a	log ₂ FC	q-value ^a	log ₂ FC	q-value ^a
1450358	-0.02	ILMN_9543	<i>HBD</i>	Homo sapiens hemoglobin, delta, mRNA.	-0.69	2.79E-02	-0.44	3.66E-01	0.26	6.76E-01
4670327	-0.11	ILMN_28646	<i>FBXO7</i>	Homo sapiens F-box protein 7, transcript variant 2, mRNA.	-0.65	1.09E-02	-0.65	5.11E-02	0.00	9.98E-01
5550452	0.07	ILMN_24236	<i>KCNMA1</i>	Homo sapiens potassium large conductance calcium-activated channel, subfamily M, alpha member 1, transcript variant 2, mRNA.	0.95	2.01E-09	1.13	1.29E-08	0.18	5.69E-01
7550066	0.00	ILMN_173016	<i>MERTK</i>	Homo sapiens c-met proto-oncogene tyrosine kinase, mRNA.	1.04	3.04E-09	1.59	1.53E-12	0.55	1.85E-02
2810767	0.45	ILMN_23396	<i>EBI3</i>	Homo sapiens Epstein-Barr virus induced 3, mRNA.	1.10	8.79E-13	0.81	1.71E-05	-0.28	2.41E-01
4040242*	0.24	ILMN_21686	<i>FAM89A</i>	Homo sapiens family with sequence similarity 89, member A, mRNA.	1.21	2.97E-14	1.56	1.42E-14	0.34	1.37E-01
3830735	0.03	ILMN_9777	<i>UPB1</i>	Homo sapiens ureidopropionase, beta, mRNA.	1.23	5.27E-13	1.67	2.14E-14	0.43	6.51E-02
7400747	0.22	ILMN_21686	<i>FAM89A</i>	Homo sapiens family with sequence similarity 89, member A, mRNA.	1.26	7.65E-14	1.65	1.13E-14	0.40	9.38E-02

Array ID	Elastic net co-efficient	Transcript ID	Official Symbol (HGNC)	Definition	Definite Bacterial vs. Definite Viral		Definite Bacterial vs Healthy Control		Definite Viral vs Healthy Control	
					log ₂ FC	q-value ^a	log ₂ FC	q-value ^a	log ₂ FC	q-value ^a
2510356	0.02	ILMN_12984	<i>EMR1</i>	Homo sapiens egf-like module containing, mucin-like, hormone receptor-like 1, mRNA.	1.33	1.50E-11	1.32	6.00E-08	-0.01	9.91E-01
3850647	0.14	ILMN_137356	<i>PTPN20</i>	PREDICTED: Homo sapiens protein tyrosine phosphatase, non-receptor type 20, mRNA.	1.35	1.88E-11	1.98	2.35E-14	0.63	1.77E-02
3830762	0.04	ILMN_30233	<i>TMEM119</i>	Homo sapiens transmembrane protein 119, mRNA.	1.35	1.76E-08	2.10	8.55E-12	0.74	2.07E-02
2140707	0.08	ILMN_28045	<i>SLPI</i>	Homo sapiens secretory leukocyte peptidase inhibitor, mRNA.	1.84	2.44E-12	2.78	4.34E-16	0.94	4.79E-03
1510424	0.06	ILMN_23476	<i>S100P</i>	Homo sapiens S100 calcium binding protein P, mRNA.	2.35	1.39E-16	2.91	6.99E-16	0.56	1.85E-01
1050168	0.03	ILMN_13685	<i>P13</i>	Homo sapiens peptidase inhibitor 3, skin-derived, mRNA.	2.58	4.52E-10	0.77	2.39E-01	-1.82	3.76E-04

* Transcripts that comprise the 2-transcript DRS signature.

HGNC = HUGO Gene Nomenclature Committee, FC = Fold Change.

^a This is the P-value corrected for false discovery, using Benjamin-Hochberg [38], for the difference in expression between the 2 comparator groups for each transcript using a moderated t-test in R using *limma* [39].

Table 5. Diagnostic performance of the bacterial vs. viral 38-transcript elastic net and DRS 2-transcript signatures in the training, test and IRIS validation datasets.

	Training Set	Test Set	IRIS Validation Set
Definite Bacterial patients (n)	42	10	23
Definite Viral patients (n)	73	19	28
38-transcript signature derived from elastic net model			
Area under ROC curve	98.9	99.5	97.8
(95% CI)	(97.4 - 99.9)	(96.8 - 100.0)	(93.8 - 100.0)
Sensitivity %	92.9	100.0	100.0
(95% CI)	(83.3 - 100.0)	(100.0 - 100.0)	(100.0 - 100.0)
Specificity %	97.3	94.7	85.71
(95% CI)	(93.2 - 100.0)	(84.2 - 100.0)	(71.4 - 96.4)
2-transcript signature derived from DRS model			
Area under ROC curve	95.5	96.3	97.4
(95% CI)	(91.8 - 98.4)	(87.4 - 100.0)	(91.2 - 100.0)
Sensitivity %	85.7	90.0	100.0
(95% CI)	(73.8 - 95.2)	(70.0 - 100.0)	(100.0 - 100.0)
Specificity %	84.9	100	96.4
(95% CI)	(76.7 - 91.8)	(100.0 - 100.0)	(89.3 - 100.0)

Table 6. GO biological process terms analysis.

Overrepresentation test for the genes in the 38-transcript signature for the GO: biological process Homo sapiens terms using the PANTHER Pathway resource (Bonferroni corrected). [48, 49]

GO Term (Biological Process)	Number of genes mapped		Expected value ^c	Over (+) or under (-) representation ^d	Fold enrichment ^e	P-value ^f	Genes associated with the GO Term
	Background Reference ^a	Signature ^b					
Cellular response to interferon-alpha (GO:0035457)	9	3	0.01	+	> 5	3.09E-03	IFIT2; OAS1; IFIT3
Response to interferon- alpha (GO:0035455)	18	4	0.03	+	> 5	1.53E-04	IFIT2; OAS1; IFIT3; EIF2AK2
Oxygen transport (GO:0015671)	15	3	0.02	+	> 5	1.42E-02	HBD; HBM; HBZ
Gas transport (GO:0015669)	19	3	0.03	+	> 5	2.88E-02	HBD; HBM; HBZ
Negative regulation of viral genome replication (GO:0045071)	46	5	0.07	+	> 5	7.86E-05	SLPI; IFIT1; OAS1; RSAD2; EIF2AK2
Type I interferon signalling pathway (GO:0060337)	68	7	0.1	+	> 5	9.68E-08	IFIT2; IFIT1; OAS1; IFI27; RSAD2; IFI6; IFIT3
Cellular response to type I interferon (GO:0071357)	68	7	0.1	+	> 5	9.68E-08	IFIT2; IFIT1; OAS1; IFI27; RSAD2; IFI6; IFIT3

GO Term (Biological Process)	Number of genes mapped	Expected value ^c	Over (+) or under (-) representation ^d	Fold enrichment ^e	P-value ^f	Genes associated with the GO Term
Response to type I interferon (GO:0034340)	69	0.11	+	> 5	1.07E-07	IFIT2; IFIT1; OAS1; IFI27; RSAD2; IFI6; IFIT3
Regulation of viral genome replication (GO:0045069)	70	0.11	+	> 5	6.25E-04	SLPI; IFIT1; OAS1; RSAD2; EIF2AK2
Negative regulation of viral life cycle (GO:1903901)	84	0.13	+	> 5	1.53E-03	SLPI; IFIT1; OAS1; RSAD2; EIF2AK2
Negative regulation of viral process (GO:0048525)	87	0.13	+	> 5	1.82E-03	SLPI; IFIT1; OAS1; RSAD2; EIF2AK2
Defence response to virus (GO:0051607)	159	0.24	+	> 5	3.36E-05	IFIT2; IFIT1; OAS1; IFI44L; RSAD2; EIF2AK2; IFIT3
Negative regulation of multi-organism process (GO:0043901)	150	0.23	+	> 5	2.59E-02	SLPI; IFIT1; OAS1; RSAD2; EIF2AK2
Response to virus (GO:0009615)	240	0.37	+	> 5	5.51E-04	IFIT2; IFIT1; OAS1; IFI44L; RSAD2; EIF2AK2; IFIT3
Defence response to other organism (GO:0098542)	371	0.57	+	> 5	5.69E-04	SLPI; IFIT2; IFIT1; OAS1; IFI44L; RSAD2; EIF2AK2; IFIT3

GO Term (Biological Process)	Number of genes mapped	Expected value ^c	Over (+) or under (-) representation ^d	Fold enrichment ^e	P-value ^f	Genes associated with the GO Term	
Background Reference ^a		Signature ^b					
Immune effector process (GO:0002252)	447	8	0.69	+	> 5	2.33E-03	IFIT2; IFIT1; OAS1; IFI44L; RSAD2; EIF2AK2; SERPING1; IFIT3
Cytokine-mediated signalling pathway (GO:0019221)	487	8	0.75	+	> 5	4.44E-03	IFIT2; IFIT1; OAS1; IFI27; RSAD2; IFI6; IFIT3; EBI3
Cellular response to cytokine stimulus (GO:0071345)	632	8	0.97	+	> 5	3.07E-02	IFIT2; IFIT1; OAS1; IFI27; RSAD2; IFI6; IFIT3; EBI3
Response to cytokine (GO:0034097)	730	9	1.12	+	> 5	8.40E-03	IFIT2; IFIT1; OAS1; IFI27; RSAD2; IFI6; EIF2AK2; IFIT3; EBI3
Innate immune response (GO:0045087)	1012	10	1.56	+	> 5	1.38E-02	IFIT2; IFIT1; OAS1; IFI27; RSAD2; IFI6; EIF2AK2; SERPING1; IFIT3; FCER1A
Immune response (GO:0006955)	1430	14	2.2	+	> 5	5.82E-05	SLPI; IFIT2; IFIT1; EMR1; OAS1; IFI44L; IFI27; RSAD2; IFI6; EIF2AK2; IFIT3; SERPING1; EBI3; FCER1A

GO Term (Biological Process)	Number of genes mapped	Expected value ^c	Over (+) or under (-) representation ^d	Fold enrichment ^e	P-value ^f	Genes associated with the GO Term
Defence response (GO:0006952)	1507	2.32	+	> 5	9.19E-03	SLPI; IFIT2; IFIT1; OAS1; IFI27; IFI44L; RSAD2; IFI6; EIF2AK2; SERPING1; IFIT3; FCER1A
Immune system process (GO:0002376)	2163	3.33	+	4.81	1.67E-04	SLPI; IFIT2; HBZ; IFIT1; EMR1; MERTK; OAS1; IFI44L; IFI27; RSAD2; IFI6; EIF2AK2; IFIT3; SERPING1; EBI3; FCER1A;
Unclassified (Unclassified)	4272	6.57	-	0.91	0.00E+00	GYPB; EPSTI1; FAM89A; MAP3K7CL; GYPE; IFIT1B

^a number of genes mapped to GO terms when using the background reference dataset of Homo Sapiens. The total number of genes in this dataset is 20814.

^b number of genes mapped to GO terms when using genes in the 38-transcript signature. The total number of genes in the signature is 36.

^c number of genes expected to be in signature for this category, based on the background reference dataset.

^d + indicates an over-representation of the GO term in the signature, - indicates an under-representation of the GO term in the signature.

^e GO term over-represented if > 1, under-represented if < 1

^f Probability that the number of genes from the signature in the GO term occurred randomly.

Table 7. Additional validation and external microarray datasets. Overview of the gene expression microarray datasets used for assessment of the 2-transcript DRS signature. Study and experimental details, as well as the metrics for classification accuracy (i.e. Sensitivity, Specificity and AUC with 95% CIs) are shown.

Results after application of the 2-transcript DRS signature									
1 st group	2 nd group	GEO accession	Reference	Age (years)	Platform	Sensitivity % (95%CI)	Specificity % (95%CI)	AUC % (95%CI)	Related eFigure
Meningococcal validation: 24 children	Viral group of the IRIS validation set (after data merging)	GSE80496	Unpublished	<3	Illumina Ref8-V3	91.7 (79.2-100)	96.0 (88.0-100)	92.6 (81.3-100)	Fig 11
Inflammatory validation: 30 JIA & 18 HSP	20% Discovery Bacterial set (after data merging)	GSE80412	Unpublished	<18	Illumina HT12-V4	90.0 (70.0-100)	95.8 (89.6-100)	90.8 (73-100)	Fig 12
48 bacterial: (S.aureus, streptococcus)	31 Pediatric SLE	GSE22098	Berry M (2010) [13]	<17	Illumina HT12-V3	93.5 (83.9-100)	96.1 (90.2-100)	96.6 (91.9-100)	Fig 12
12 bacterial (S.pneumoniae, S.aureus)	10 viral (Influenza A and B)	GSE6269 – GPL570	Ramilo O (2007)[11]	<16	Affymetrix	100 (100-100)	90 (70-100)	96 (85-100)	Fig 12
8 bacterial – mixed gram positive & gram negative	22 viral – mixed adenovirus, HHV6, enterovirus	GSE40396	Hu X (2013) [12]	<3	Illumina HT12-V4	100 (100-100)	77.3 (59.1-95.5)	89.2 (75.6-98.3)	Fig 12
15 bacterial LTRI	64 Viral LTRI	GSE60244	Suarez N (2015) [14]	Adults	Illumina HT12-V4	90.1 (77.3-100)	80.3 (70.4-88.7)	89.8 (83.4-95.5)	Fig 12

Table 8. Performance of clinical features in relation to DRS score in patients with indeterminate infection status (combined Probable Bacterial, Unknown, and Probable Viral groups).

	Patients split by DRS score		P value
	DRS predicts viral infection	DRS predicts bacterial infection	
Number of patients	95	80	
Shock (needed inotropes)	22 of 95	35 of 80	0.006
%	(23%)	(44%)	
Respiratory failure requiring ventilation	46 of 95	51 of 80	0.048
%	(48%)	(64%)	
Requiring intensive care admission	51 of 95	54 of 80	0.066
%	(54%)	(68%)	
White blood count ($\times 10^3/\text{mm}^3$): median	11.1	14.1	0.079
(IQR) ^a	(7.3-16.0)	(8.3-19.4)	
Neutrophil count ($\times 10^3/\text{mm}^3$): median	6.8	8.7	0.114
(IQR) ^a	(3.5-11.4)	(5.0-13.8)	
CRP during illness (mg/l) ^a	71	101	0.015
(IQR)	(27-120)	(48-192)	
Respiratory infection: CXR consolidation	43 of 69	47 of 66	0.3612
%	(62%)	(71%)	
Respiratory infection: no CXR focal change	24 of 69	18 of 66	0.3599
%	(35%)	(27%)	

^a with available data. Maximum values in illness used.

IQR – interquartile range; CRP – C reactive protein; CXR – chest X-ray

Clinical features of children in the three indeterminate groups (Probable Bacterial, Unknown and Probable Viral) were classified. For each clinical feature, the proportion of children with a DRS predictive of viral or of bacterial infection was compared using Fisher exact test and two tailed t-tests. DRS predictive of bacterial infection was significantly associated with shock, ventilation and higher CRP.

Table 9 – Sequences of probes in 38 and 2 transcript gene signatures

Array ID	Transcript ID	Entrez Symbol	Sequence (5' to 3')
3990170	ILMN_17548	<i>IFI27</i>	CCAAGTTCATCCTGGGCTCCATTGGGTCTGCCATTGCGGCTGT CATTGCG (SEQ ID NO: 3)
3870338*	ILMN_9752	<i>IFI44L</i>	GTGGGCTAAGATAGGTCTACTGCAAACCAACCCCTCCATATTT CCGTACC (SEQ ID NO: 4)
2000148	ILMN_1751	<i>IFIT1</i>	TGAATGAAGCCCTGGAGTACTATGAGCGGGCCCTGAGACTGG CTGCTGAC (SEQ ID NO: 5)
3360343	ILMN_37168	<i>RSAD2</i>	CGCTGGAACCTTGGGCAAGGAAGAATGTGAGCAAGAGTAGA GAGAGTGCC (SEQ ID NO: 6)
6510170	ILMN_22925	<i>IFIT3</i>	AAAACAAAATCAACCGGGACCCAGCTTTTCAGAACTGCAGG GAAACAGC (SEQ ID NO: 7)
520408	ILMN_1944	<i>IFIT3</i>	ACAAATCAGCCTGGTCACCAGCTTTTCGGAACAGCAGAGACA CAGAGGGC (SEQ ID NO: 8)
1440615	ILMN_27303	<i>OTOF</i>	GCCCGTCAAGTGCTGCCCTGCCTGTGTCTGGGTTTCTGTTGG CTGTTTT (SEQ ID NO: 9)
2600747	ILMN_28123	<i>IFIT2</i>	GCTGACCCAGCATCAGCCACACTCTGGGTTGGAAAATGTTTGC CTGTTGG (SEQ ID NO: 10)
5700725	ILMN_27754	<i>EPSTI1</i>	GGGAGTCACTTGATGCTTTCAGGTTAATCAGAGCTATGGGTG CTACAGGC (SEQ ID NO: 11)
2030309	ILMN_15074	<i>SERPING1</i>	TGGGACCAGCAGCACAAGTTCCTGTCTTCATGGGGCGAGTA TATGACCC (SEQ ID NO: 12)
1090390	ILMN_2717	<i>OAS1</i>	AGAGAGACTTCCTGAAGCAGCGCCCCACCAAGCTCAAGAGCC TCATCCGC (SEQ ID NO: 13)
5090215	ILMN_13978	<i>IFI6</i>	TGCGCCGACGATGCCCAGAATCCAGAACTTTGTCTATCACTCT CCCCAAC (SEQ ID NO: 14)
620544	ILMN_5312	<i>HLA-DRB6</i>	AACCCACAGCCTTGATGGCAGCGCCTCGTCTCAACTTTTGT GCTTCCT (SEQ ID NO: 15)
6980192	ILMN_19775	<i>HBZ</i>	GTCCTGGAGGTTCCCGAGCCCACTTACCGCGTAATGCGCCAA TAAACCA (SEQ ID NO: 16)
1030100	ILMN_89157	<i>HS.386275</i>	TGTTCTTCCCATGTCCTGGATGCCACTGGAAGTGCACACTGC TTGTATG (SEQ ID NO: 17)
2120079	ILMN_168435	<i>EIF2AK2</i>	CGTTCTCTGCCTCACATAGCTTACAAGCCAGCTGGAGAAATAT GGTACTC (SEQ ID NO: 18)
3780452	ILMN_5646	<i>IFIT1L</i>	AGGCCTTGTGGCACCAGACATAAGACCCCTGAAAGTATCATC CCTCCTG (SEQ ID NO: 19)
3360615	ILMN_18288	<i>FCER1A</i>	GAACCAGGAAAGGCTTCAGACTTCTGAACCCACATCCTAAGCC AAACCCC (SEQ ID NO: 20)
150315	ILMN_9078	<i>C21ORF7</i>	GTGACCTCACAGTAAACATCTCTGCCTTTCCTGTGTGTGTTCT GGGGGA (SEQ ID NO: 21)
6940086	ILMN_21264	<i>GYPE</i>	AGGATGTGGCCTGCATGCTGCCTGATCTGCCTAGAACCAGCT GCACCTG (SEQ ID NO: 22)
3780187	ILMN_27651	<i>GYPB</i>	TGGAGAAACGGGACAACCTTGCCATCGTTTCACTGTACCAGCT CCTGTAG (SEQ ID NO: 23)
4480730	ILMN_2819	<i>HBM</i>	TCGTGCTGCGCGTGGACCCAGCCAACCTTCCGCTGCTAATCCA GTGTTTC (SEQ ID NO: 24)
4150600	ILMN_14704	<i>EIF1AY</i>	CTGAGGATGGTTCTACAGTTGGGATTTTGGCCATCATCAACCA AGAAGAG (SEQ ID NO: 25)

Array ID	Transcript ID	Entrez Symbol	Sequence (5' to 3')
1010546	ILMN_43805	<i>LOC649143</i>	GGTTGGTGAGAGCTTCACAGTGCAGAGGCGAGTCCATCCTGA GGTGACTG (SEQ ID NO: 26)
1450358	ILMN_9543	<i>HBD</i>	GGCTAATGCCCTGGCTCACAAGTACCATTGAGATCCTGGACTG TTTCCTG (SEQ ID NO: 27)
4670327	ILMN_28646	<i>FBXO7</i>	AGGCGACGGGAAGCGCGGGTGGTCGGCTGGGGTCCGGCTCC TGGAGAACA (SEQ ID NO: 28)
5550452	ILMN_24236	<i>KCNMA1</i>	GGTTCTGCATGACCTAGCCACTGCTGGGGGTTTTCTTCTATAA CGTTGTC (SEQ ID NO: 29)
7550066	ILMN_173016	<i>MERTK</i>	CTTCCTTACCAAGTGAATCCATGGCCCCAAAGCACCAGATGA ATGTTGT (SEQ ID NO: 30)
2810767	ILMN_23396	<i>EBI3</i>	GAGCTGCCGGGCAACCTCAGATGACCGACTTTTCCCTTTGAGC CTCAGT (SEQ ID NO: 31)
4040242*	ILMN_21686	<i>FAM89A</i>	CAGGGGATGAGCGCTACCAGTTTCATTTGTAGGCAGGGAGTT CTCCGCGG (SEQ ID NO: 32)
3830735	ILMN_9777	<i>UPB1</i>	GAAATTCTGCCTGAGGACAGCAGCCCAGTGCTTGCGAGAGT TCCTGACA (SEQ ID NO: 33)
7400747	ILMN_21686	<i>FAM89A</i>	GATCTCGGTGAAAGGCCTTAGTGGGTGTTTTGTGTGAGGTGG CTGTAGC (SEQ ID NO: 34)
2510356	ILMN_12984	<i>EMR1</i>	TCTCAGCTTAACATGGAAATGAGGATCCCACCAGCCCCAGAAC CCTCTGG (SEQ ID NO: 35)
3850647	ILMN_137356	<i>PTPN20</i>	GCATCCTGAGGTGGCCAAGGGCAGTGGTGCTCCAGATGTTTC TGTTTCTG (SEQ ID NO: 36)
3830762	ILMN_30233	<i>TMEM119</i>	GTCTGGCAGCCTGTGTCCACAATATTCGTCAGTCCTCGACAGG GAGCCTG (SEQ ID NO: 37)
2140707	ILMN_28045	<i>SLPI</i>	GGATCCTGTTGACACCCCAACCAACAAGGAGGAAGCCTGG GAAGTGCC (SEQ ID NO: 38)
1510424	ILMN_23476	<i>S100P</i>	AATGATGCCCTGGAGATGTCACAGATTCCTGGCAGAGCCATG GTCCCAGG (SEQ ID NO: 39)
1050168	ILMN_13685	<i>PI3</i>	CTGACTGCCAGGAATCAAGAAGTGCTGTGAAGGCTCTTGCG GGATGGCC (SEQ ID NO: 40)

* Probe used in 2 transcript/gene signature

Table 10 – Performance of different 2 transcript signatures

Combi ID	Array ID	1st gene	expression level *	Array ID	2nd gene	expression level *	AUC training dataset		AUC Test dataset		AUC IRIS validation dataset		Total AUC (training+test+iris)	
							opposite^	same#	opposite^	same#	opposite^	same#	opposite^	same#
489	1090390	OAS1	DOWN	2510356	EMR1	UP	0.94032	0.65333	0.95789	0.66842	0.98609	0.70435	2.88430	2.02610
80	3870338	IFI44L	DOWN	7400747	FAM89A	UP	0.94921	0.78667	0.96316	0.60000	0.97043	0.73391	2.88280	2.12058
267	2510356	EMR1	UP	3870338	IFI44L	DOWN	0.93365	0.79524	0.97368	0.63158	0.97217	0.86261	2.87951	2.28943
467	1090390	OAS1	DOWN	7400747	FAM89A	UP	0.96063	0.69048	0.93684	0.71579	0.97913	0.59478	2.87661	2.00105
224	2810767	EBI3	UP	3870338	IFI44L	DOWN	0.93397	0.81810	0.96842	0.66316	0.97391	0.83478	2.87630	2.31604
399	1510424	S100P	UP	3360343	RSAD2	DOWN	0.94413	0.65524	0.94737	0.72105	0.98435	0.62261	2.87584	1.99890
290	2140707	SLPI	UP	3870338	IFI44L	DOWN	0.92317	0.75778	0.98947	0.61053	0.96174	0.83826	2.87439	2.20656
384	1510424	S100P	UP	5700725	EPSTI1	DOWN	0.94381	0.51968	0.96316	0.90000	0.96522	0.48348	2.87218	1.90316
392	1510424	S100P	UP	3870338	IFI44L	DOWN	0.93968	0.70063	0.95789	0.65263	0.97217	0.70087	2.86975	2.05414
477	1090390	OAS1	DOWN	4040242	FAM89A	UP	0.96159	0.70032	0.93158	0.73158	0.97565	0.70261	2.86882	2.13451
90	3870338	IFI44L	DOWN	4040242	FAM89A	UP	0.94540	0.79683	0.95789	0.59474	0.96522	0.80000	2.86851	2.19156
274	2510356	EMR1	UP	3360343	RSAD2	DOWN	0.92952	0.74952	0.95263	0.55789	0.98609	0.83478	2.86824	2.14220
632	520408	IFIT3	DOWN	7400747	FAM89A	UP	0.95016	0.69619	0.93684	0.62632	0.98087	0.66261	2.86787	1.98511
119	3830762	TMEM119	UP	3870338	IFI44L	DOWN	0.92317	0.80444	1.00000	0.48947	0.94435	0.96000	2.86752	2.25392
654	520408	IFIT3	DOWN	2510356	EMR1	UP	0.92571	0.67111	0.95789	0.57368	0.98261	0.74087	2.86622	1.98566
23	5090215	IFI6	DOWN	7400747	FAM89A	UP	0.96286	0.60444	0.96316	0.83684	0.93913	0.53913	2.86515	1.98042
12	5700725	EPSTI1	DOWN	7400747	FAM89A	UP	0.96095	0.70159	0.94211	0.68947	0.96174	0.56696	2.86480	1.95802
642	520408	IFIT3	DOWN	4040242	FAM89A	UP	0.94825	0.70540	0.93684	0.61579	0.97913	0.76000	2.86423	2.08119
134	3830735	UPB1	UP	3870338	IFI44L	DOWN	0.93619	0.80254	0.96316	0.58421	0.96348	0.92696	2.86283	2.31371
406	1510424	S100P	UP	2000148	IFIT1	DOWN	0.94571	0.67556	0.94211	0.66316	0.97391	0.70783	2.86173	2.04654
192	3360343	RSAD2	DOWN	7400747	FAM89A	UP	0.95365	0.74413	0.93158	0.50000	0.97565	0.72522	2.86088	1.96934
259	2510356	EMR1	UP	5700725	EPSTI1	DOWN	0.94000	0.67175	0.95789	0.65263	0.96174	0.69739	2.85963	2.02177
404	1510424	S100P	UP	2120079	EIF2AK2	DOWN	0.94095	0.67841	0.95263	0.98421	0.96522	0.58261	2.85880	2.24523
202	3360343	RSAD2	DOWN	4040242	FAM89A	UP	0.95016	0.75429	0.93158	0.49474	0.97565	0.81217	2.85739	2.06120
8	6510170	IFIT3	DOWN	7400747	FAM89A	UP	0.94794	0.69587	0.92632	0.56316	0.98261	0.55652	2.85686	1.81555
490	1090390	OAS1	DOWN	2140707	SLPI	UP	0.91556	0.59016	0.97895	0.89474	0.96174	0.65391	2.85624	2.13881
353	2000148	IFIT1	DOWN	7400747	FAM89A	UP	0.95397	0.76825	0.92632	0.53158	0.97391	0.76348	2.85420	2.06331
655	520408	IFIT3	DOWN	2140707	SLPI	UP	0.91524	0.63016	0.97895	0.78421	0.96000	0.70435	2.85419	2.11872
258	2510356	EMR1	UP	6510170	IFIT3	DOWN	0.92381	0.69079	0.94737	0.47368	0.98261	0.67304	2.85379	1.83752
494	1090390	OAS1	DOWN	1510424	S100P	UP	0.94095	0.51016	0.94211	0.92632	0.97043	0.54783	2.85349	1.98430
376	2000148	IFIT1	DOWN	2140707	SLPI	UP	0.92667	0.74317	0.96316	0.64737	0.96348	0.83652	2.85330	2.22706

375	2000148	IFIT1	DOWN	2510356	EMR1	UP	0.93206	0.77206	0.94211	0.60526	0.97913	0.85391	2.85330	2.23124
61	4040242	FAM89A	UP	5700725	EPST11	DOWN	0.95778	0.72095	0.94211	0.67895	0.95304	0.67130	2.85293	2.07120
297	2140707	SLPI	UP	3360343	RSAD2	DOWN	0.91746	0.71746	0.96842	0.68947	0.96696	0.77913	2.85284	2.18606
401	1510424	S100P	UP	2600747	IFIT2	DOWN	0.94444	0.46825	0.93684	0.82632	0.97043	0.65739	2.85172	1.95196
367	2000148	IFIT1	DOWN	3830762	TMEM119	UP	0.92127	0.78413	0.97895	0.50000	0.95130	0.93565	2.85152	2.21978
363	2000148	IFIT1	DOWN	4040242	FAM89A	UP	0.95048	0.77778	0.92632	0.52632	0.97391	0.81217	2.85071	2.11627
282	2140707	SLPI	UP	5700725	EPST11	DOWN	0.91587	0.60190	0.98421	0.85789	0.94957	0.64174	2.84965	2.10154
60	4040242	FAM89A	UP	6510170	IFIT3	DOWN	0.94381	0.70921	0.92632	0.56842	0.97913	0.68000	2.84926	1.95763
517	1050168	PI3	UP	3360343	RSAD2	DOWN	0.89397	0.57810	1.00000	0.73158	0.95130	0.69217	2.84527	2.00185
487	1090390	OAS1	DOWN	2810767	EBI3	UP	0.94095	0.73556	0.93158	0.70000	0.97217	0.77043	2.84471	2.20599
302	2120079	EIF2AK2	DOWN	7400747	FAM89A	UP	0.95460	0.53968	0.91053	0.87895	0.97913	0.55826	2.84426	1.97689
216	2810767	EBI3	UP	5700725	EPST11	DOWN	0.93841	0.76667	0.95263	0.65789	0.95304	0.72174	2.84409	2.14630
659	520408	IFIT3	DOWN	1510424	S100P	UP	0.94317	0.55429	0.93684	0.82632	0.96348	0.48522	2.84349	1.86582
510	1050168	PI3	UP	3870338	IF144L	DOWN	0.89778	0.63651	0.99474	0.67368	0.94957	0.80870	2.84208	2.11889
386	1510424	S100P	UP	5090215	IF16	DOWN	0.93968	0.63397	0.96842	0.97368	0.93391	0.65565	2.84202	2.26330
464	1440615	OTOF	DOWN	1510424	S100P	UP	0.92571	0.56825	0.94737	0.89474	0.96870	0.50435	2.84178	1.96734
481	1090390	OAS1	DOWN	3830762	TMEM119	UP	0.91460	0.69873	1.00000	0.76316	0.92696	0.89739	2.84156	2.35928
206	3360343	RSAD2	DOWN	3830762	TMEM119	UP	0.91905	0.76667	0.98947	0.55789	0.93043	0.95478	2.83896	2.27934
231	2810767	EBI3	UP	3360343	RSAD2	DOWN	0.92603	0.79810	0.93158	0.60000	0.98087	0.84522	2.83848	2.24331
457	1440615	OTOF	DOWN	2810767	EBI3	UP	0.92032	0.74190	0.94737	0.64737	0.97043	0.79652	2.83812	2.18579
383	1510424	S100P	UP	6510170	IFIT3	DOWN	0.94222	0.57079	0.93684	0.82105	0.95826	0.57565	2.83733	1.96750
437	1440615	OTOF	DOWN	7400747	FAM89A	UP	0.93683	0.70730	0.93158	0.65789	0.96870	0.62087	2.83710	1.98607
243	2600747	IFIT2	DOWN	4040242	FAM89A	UP	0.95079	0.70476	0.91579	0.61579	0.97043	0.80000	2.83702	2.12055
451	1440615	OTOF	DOWN	3830762	TMEM119	UP	0.92222	0.70444	1.00000	0.76842	0.91478	0.89043	2.83700	2.36330
233	2600747	IFIT2	DOWN	7400747	FAM89A	UP	0.95365	0.69270	0.91053	0.61053	0.97217	0.73913	2.83635	2.04236
68	3990170	IFIT2	DOWN	7400747	FAM89A	UP	0.94222	0.80286	0.94737	0.68421	0.94435	0.73391	2.83394	2.22098
482	1090390	OAS1	DOWN	3830735	UPB1	UP	0.93683	0.68857	0.93684	0.74737	0.96000	0.87130	2.83367	2.30724
447	1440615	OTOF	DOWN	4040242	FAM89A	UP	0.93302	0.71968	0.93684	0.67368	0.96348	0.74609	2.83334	2.13945
368	2000148	IFIT1	DOWN	3830735	UPB1	UP	0.93111	0.78889	0.93684	0.56842	0.96522	0.90435	2.83317	2.26166
530	1030100	HS.386275	DOWN	7400747	FAM89A	UP	0.94921	0.55460	0.90000	0.87895	0.98261	0.62957	2.83182	2.06312
312	2120079	EIF2AK2	DOWN	4040242	FAM89A	UP	0.95079	0.55238	0.90526	0.86842	0.97565	0.66609	2.83171	2.08689
207	3360343	RSAD2	DOWN	3830735	UPB1	UP	0.92603	0.76952	0.93684	0.52105	0.96696	0.92174	2.82983	2.21232
524	1050168	PI3	UP	2000148	IFIT1	DOWN	0.89429	0.60413	0.98947	0.64737	0.94435	0.74957	2.82811	2.00106
652	520408	IFIT3	DOWN	2810767	EBI3	UP	0.91778	0.74222	0.92632	0.56316	0.98261	0.80000	2.82670	2.10538
299	2140707	SLPI	UP	2600747	IFIT2	DOWN	0.91683	0.61079	0.95789	0.78421	0.95130	0.77043	2.82602	2.16544
460	1440615	OTOF	DOWN	2140707	SLPI	UP	0.89048	0.67365	0.97895	0.88421	0.95652	0.65739	2.82595	2.21525

281	2140707	SLPI	UP	6510170	IFIT3	DOWN	0.90952	0.64825	0.97895	0.74211	0.93739	0.58783	2.82586	1.97819
276	2510356	EMR1	UP	2600747	IFIT2	DOWN	0.92857	0.65587	0.92105	0.58947	0.97565	0.81913	2.82528	2.06448
550	1030100	HS.386275	DOWN	2810767	EBI3	UP	0.93206	0.60825	0.91579	0.89474	0.97739	0.61739	2.82524	2.12038
545	1030100	HS.386275	DOWN	3830735	UPB1	UP	0.93651	0.48476	0.92632	0.90526	0.96000	0.67652	2.82282	2.06655
647	520408	IFIT3	DOWN	3830735	UPB1	UP	0.92381	0.69492	0.93684	0.63158	0.96174	0.87652	2.82239	2.20302
553	1030100	HS.386275	DOWN	2140707	SLPI	UP	0.90698	0.46413	0.96842	0.96842	0.94609	0.61043	2.82149	2.04298
63	4040242	FAM89A	UP	5090215	IFI6	DOWN	0.96508	0.62254	0.95263	0.81579	0.90261	0.57217	2.82032	2.01050
540	1030100	HS.386275	DOWN	4040242	FAM89A	UP	0.94921	0.56952	0.90000	0.87895	0.97043	0.49217	2.81964	1.94065
289	2140707	SLPI	UP	3990170	IFI27	DOWN	0.92254	0.81111	0.95789	0.56842	0.93913	0.78609	2.81956	2.16562
105	3850647	PTPN20	UP	3870338	IFI44L	DOWN	0.93143	0.78603	0.93158	0.56842	0.95652	0.96522	2.81953	2.31967
452	1440615	OTOI	DOWN	3830735	UPB1	UP	0.92730	0.70476	0.93684	0.71053	0.95478	0.85217	2.81893	2.26746
557	1030100	HS.386275	DOWN	1510424	S100P	UP	0.93746	0.67587	0.93684	0.99474	0.94435	0.76696	2.81865	2.43757
391	1510424	S100P	UP	3990170	IFI27	DOWN	0.93016	0.73079	0.96842	0.52105	0.92000	0.66261	2.81858	1.91445
317	2120079	EIF2AK2	DOWN	3830735	UPB1	UP	0.91206	0.50825	0.94737	0.90526	0.95826	0.79304	2.81769	2.20656
325	2120079	EIF2AK2	DOWN	2140707	SLPI	UP	0.89143	0.56063	0.97368	0.95789	0.95130	0.44870	2.81642	1.96723
223	2810767	EBI3	UP	3990170	IFI27	DOWN	0.94095	0.84190	0.95263	0.70000	0.92174	0.83304	2.81532	2.37495
85	3870338	IFI44L	DOWN	5550452	KCNMA1	UP	0.92508	0.82254	0.93158	0.65263	0.95826	0.94435	2.81492	2.41952
111	3830762	TMEM119	UP	5700725	EPSTI1	DOWN	0.91048	0.70984	0.99474	0.72632	0.90957	0.88870	2.81478	2.32485
247	2600747	IFIT2	DOWN	3830762	TMEM119	UP	0.90190	0.70349	0.97368	0.67895	0.93913	0.92348	2.81472	2.30592
284	2140707	SLPI	UP	5090215	IFI6	DOWN	0.90317	0.50857	0.98421	0.95789	0.92696	0.51304	2.81434	1.97951
646	520408	IFIT3	DOWN	3830762	TMEM119	UP	0.90190	0.72095	0.98421	0.66842	0.92696	0.90609	2.81307	2.29546
126	3830735	UPB1	UP	5700725	EPSTI1	DOWN	0.93270	0.70603	0.94737	0.71579	0.93217	0.84000	2.81224	2.26182
78	3990170	IFI27	DOWN	4040242	FAM89A	UP	0.94254	0.81302	0.94211	0.67368	0.92522	0.78261	2.80986	2.26931
373	2000148	IFIT1	DOWN	2810767	EBI3	UP	0.92635	0.80730	0.90526	0.59474	0.97739	0.85043	2.80900	2.25247
205	3360343	RSAD2	DOWN	3850647	PTPN20	UP	0.92889	0.74984	0.92105	0.46842	0.95826	0.96522	2.80820	2.18348
215	2810767	EBI3	UP	6510170	IFIT3	DOWN	0.91492	0.76413	0.92105	0.50526	0.97217	0.73913	2.80815	2.00852
79	3870338	IFI44L	DOWN	7550066	MERTK	UP	0.92730	0.81270	0.91579	0.64737	0.96348	0.90783	2.80657	2.36789
218	2810767	EBI3	UP	5090215	IFI6	DOWN	0.93810	0.67524	0.96316	0.83158	0.90261	0.64174	2.80386	2.14856
133	3830735	UPB1	UP	3990170	IFI27	DOWN	0.94825	0.80984	0.95789	0.72105	0.89565	0.86087	2.80180	2.39176
509	1050168	PI3	UP	3990170	IFI27	DOWN	0.91143	0.69873	0.96842	0.70526	0.92174	0.71478	2.80159	2.11878
248	2600747	IFIT2	DOWN	3830735	UPB1	UP	0.92730	0.68508	0.92105	0.64737	0.95130	0.88870	2.79966	2.22114
544	1030100	HS.386275	DOWN	3830762	TMEM119	UP	0.90698	0.56635	0.96316	0.90526	0.92870	0.72696	2.79884	2.19857
118	3830762	TMEM119	UP	3990170	IFI27	DOWN	0.92413	0.82762	0.98421	0.53158	0.88870	0.89217	2.79703	2.25137
253	2600747	IFIT2	DOWN	2810767	EBI3	UP	0.92159	0.74222	0.91579	0.57368	0.95826	0.82957	2.79564	2.14547
110	3830762	TMEM119	UP	6510170	IFIT3	DOWN	0.90381	0.71905	0.97895	0.64211	0.91130	0.83652	2.79406	2.19767
232	2600747	IFIT2	DOWN	7550066	MERTK	UP	0.92952	0.69968	0.91053	0.43158	0.95304	0.87478	2.79309	2.00604

322	2120079	EIF2AK2	DOWN	2810767	EBI3	UP	0.91175	0.59810	0.91053	0.92632	0.97043	0.72000	2.79271	2.24441
405	1510424	S100P	UP	2030309	SERPING1	DOWN	0.91397	0.54063	0.93158	0.86842	0.94609	0.64174	2.79163	2.05080
695	150315	C21ORF7	DOWN	1510424	S100P	UP	0.89397	0.70317	0.96316	0.97368	0.93391	0.76696	2.79104	2.44382
542	1030100	H3.386275	DOWN	3870338	IFI44L	DOWN	0.86032	0.90825	0.97895	0.77895	0.94957	0.95826	2.78883	2.64546
191	3360343	RSAD2	DOWN	7550066	MERTK	UP	0.92127	0.77429	0.90526	0.58947	0.96174	0.89565	2.78827	2.25941
631	520408	IFIT3	DOWN	7550066	MERTK	UP	0.92286	0.70063	0.90526	0.56316	0.96000	0.85913	2.78812	2.12292
663	520408	IFIT3	DOWN	1050168	PI3	UP	0.89016	0.51841	0.96316	0.78947	0.93391	0.60696	2.78723	1.91484
125	3830735	UPB1	UP	6510170	IFIT3	DOWN	0.91460	0.71810	0.92632	0.58421	0.94609	0.80870	2.78701	2.11100
528	1050168	PI3	UP	1090390	OAS1	DOWN	0.87968	0.55841	0.97895	0.85263	0.92696	0.54261	2.78559	1.95365
466	1090390	OAS1	DOWN	7550066	MERTK	UP	0.93651	0.68349	0.88421	0.65789	0.96348	0.84522	2.78420	2.18660
104	3850647	PTPN20	UP	3990170	IFIT2	DOWN	0.94095	0.78190	0.94737	0.68421	0.89391	0.88348	2.78223	2.34959
327	2030309	SERPING1	DOWN	7400747	FAM89A	UP	0.91587	0.67143	0.92105	0.66316	0.94435	0.52000	2.78127	1.85459
261	2510356	EMR1	UP	5090215	IFI6	DOWN	0.93302	0.53333	0.96316	0.76316	0.88348	0.56522	2.77965	1.86171
352	2000148	IFIT1	DOWN	7550066	MERTK	UP	0.92190	0.79619	0.89474	0.61579	0.96000	0.91652	2.77664	2.32850
501	1050168	PI3	UP	6510170	IFIT3	DOWN	0.88540	0.50032	0.98421	0.76842	0.90609	0.49391	2.77569	1.76265
645	520408	IFIT3	DOWN	3850647	PTPN20	UP	0.91175	0.69270	0.91579	0.66842	0.94783	0.95304	2.77536	2.31416
21	5550452	KCNMA1	UP	5700725	EPSTI1	DOWN	0.92603	0.76921	0.90526	0.65263	0.94261	0.84174	2.77390	2.26358
637	520408	IFIT3	DOWN	5550452	KCNMA1	UP	0.91905	0.72984	0.90526	0.53158	0.94783	0.91130	2.77214	2.17272
519	1050168	PI3	UP	2600747	IFIT2	DOWN	0.88349	0.53968	0.95263	0.79474	0.93565	0.71652	2.77178	2.05094
337	2030309	SERPING1	DOWN	4040242	FAM89A	UP	0.91556	0.68254	0.92105	0.67368	0.93217	0.56696	2.76878	1.92318
197	3360343	RSAD2	DOWN	5550452	KCNMA1	UP	0.91873	0.79556	0.89474	0.60000	0.95478	0.93739	2.76825	2.33295
314	2120079	EIF2AK2	DOWN	3870338	IFI44L	DOWN	0.89556	0.89460	0.94211	0.78947	0.92870	0.94783	2.76636	2.63190
358	2000148	IFIT1	DOWN	5550452	KCNMA1	UP	0.92444	0.81524	0.89474	0.61053	0.94609	0.92696	2.76527	2.35272
324	2120079	EIF2AK2	DOWN	2510356	EMR1	UP	0.90508	0.53143	0.89474	0.83158	0.96348	0.63826	2.76329	2.00127
238	2600747	IFIT2	DOWN	5550452	KCNMA1	UP	0.92349	0.72698	0.88421	0.55789	0.95478	0.91304	2.76249	2.19792
316	2120079	EIF2AK2	DOWN	3830762	TMEM119	UP	0.88032	0.58032	0.97895	0.88421	0.90261	0.85217	2.76187	2.31670
84	3870338	IFI44L	DOWN	5700725	EPSTI1	DOWN	0.87333	0.90063	0.94737	0.81579	0.94087	0.94783	2.76157	2.66425
480	1090390	OAS1	DOWN	3850647	PTPN20	UP	0.92381	0.66317	0.91053	0.78421	0.92522	0.93565	2.75955	2.38304
472	1090390	OAS1	DOWN	5550452	KCNMA1	UP	0.93556	0.74000	0.88421	0.68947	0.93739	0.90783	2.75716	2.33730
527	1050168	PI3	UP	1440615	OTOF	DOWN	0.86889	0.47651	0.94737	0.86316	0.93913	0.56870	2.75539	1.90836
97	3850647	PTPN20	UP	5700725	EPSTI1	DOWN	0.92444	0.70413	0.91053	0.73158	0.92000	0.92000	2.75497	2.35571
436	1440615	OTOF	DOWN	7550066	MERTK	UP	0.91683	0.71302	0.88947	0.60000	0.94783	0.84348	2.75413	2.15649
366	2000148	IFIT1	DOWN	3850647	PTPN20	UP	0.92889	0.78095	0.87895	0.52632	0.94609	0.94087	2.75392	2.24814
350	2030309	SERPING1	DOWN	2140707	SLPI	UP	0.89143	0.61873	0.95263	0.80526	0.90957	0.52696	2.75363	1.95095
128	3830735	UPB1	UP	5090215	IFI6	DOWN	0.93111	0.44698	0.95263	0.85263	0.86609	0.67652	2.74983	1.97614
442	1440615	OTOF	DOWN	5550452	KCNMA1	UP	0.90825	0.76349	0.90526	0.62632	0.93391	0.89043	2.74743	2.28024

502	1050168	PI3	UP	5700725	EP5T11	DOWN	0.87111	0.54317	0.97368	0.82105	0.90261	0.54087	2.74740	1.90510
459	1440615	OTOF	DOWN	2510356	EMR1	UP	0.90635	0.69778	0.86842	0.67368	0.97043	0.74783	2.74521	2.11929
7	6510170	IFIT3	DOWN	7550066	MERTK	UP	0.91048	0.72540	0.90000	0.51579	0.93043	0.79304	2.74091	2.03423
535	1030100	HS.386275	DOWN	5550452	KCNMA1	UP	0.92952	0.61714	0.85263	0.86316	0.95826	0.76696	2.74042	2.24726
11	5700725	EP5T11	DOWN	7550066	MERTK	UP	0.92159	0.72857	0.88421	0.66316	0.93391	0.79826	2.73971	2.18999
266	2510356	EMR1	UP	3990170	IFI27	DOWN	0.93143	0.79651	0.92105	0.68947	0.88696	0.82609	2.73944	2.31207
96	3850647	PTPN20	UP	6510170	IFI73	DOWN	0.91556	0.69841	0.91053	0.64737	0.91304	0.90435	2.73913	2.25013
552	1030100	HS.386275	DOWN	2510356	EMR1	UP	0.91937	0.51683	0.86316	0.87368	0.95652	0.55130	2.73904	1.94181
246	2600747	IFIT2	DOWN	3850647	PTPN20	UP	0.90825	0.69333	0.88421	0.69474	0.94609	0.93739	2.73855	2.32546
73	3990170	IFI27	DOWN	5550452	KCNMA1	UP	0.92921	0.84159	0.92632	0.78947	0.87478	0.90261	2.73030	2.53367
301	2120079	EIF2AK2	DOWN	7550066	MERTK	UP	0.89873	0.53238	0.87895	0.84211	0.95130	0.79130	2.72898	2.16579
450	1440615	OTOF	DOWN	3850647	PTPN20	UP	0.90635	0.71302	0.90000	0.70526	0.92174	0.93043	2.72809	2.34871
307	2120079	EIF2AK2	DOWN	5550452	KCNMA1	UP	0.91333	0.60444	0.88947	0.83158	0.91826	0.85391	2.72107	2.28994
86	3870338	IFI44L	DOWN	5090215	IFI6	DOWN	0.89365	0.90063	0.91579	0.80526	0.91130	0.93913	2.72074	2.64503
67	3990170	IFI27	DOWN	7550066	MERTK	UP	0.92794	0.83619	0.91579	0.73684	0.87652	0.85739	2.72025	2.43042
349	2030309	SERPING1	DOWN	2510356	EMR1	UP	0.90095	0.65905	0.88421	0.66316	0.93391	0.45565	2.71908	1.77786
691	150315	C21ORF7	DOWN	2140707	SLPI	UP	0.86190	0.61651	0.96842	0.97368	0.88870	0.57043	2.71902	2.16063
347	2030309	SERPING1	DOWN	2810767	EBI3	UP	0.89810	0.71556	0.90526	0.67895	0.91478	0.62783	2.71814	2.02233
20	5550452	KCNMA1	UP	6510170	IFIT3	DOWN	0.91937	0.74286	0.86316	0.50526	0.92870	0.84696	2.71122	2.09508
523	1050168	PI3	UP	2030309	SERPING1	DOWN	0.87143	0.52540	0.97368	0.81053	0.86087	0.59652	2.70598	1.93244
549	1030100	HS.386275	DOWN	3360343	RSAD2	DOWN	0.84730	0.90000	0.92105	0.76842	0.93043	0.96348	2.69879	2.63190
341	2030309	SERPING1	DOWN	3830762	TMEM119	UP	0.88603	0.68222	0.98421	0.76316	0.82609	0.71652	2.69633	2.16190
398	1510424	S100P	UP	3360615	FCER1A	DOWN	0.86413	0.71778	0.94211	0.98421	0.88348	0.84348	2.68971	2.54547
113	3830762	TMEM119	UP	5090215	IFI6	DOWN	0.89111	0.61492	1.00000	0.85263	0.79826	0.76696	2.68937	2.23451
561	1030100	HS.386275	DOWN	1050168	PI3	UP	0.85397	0.63206	0.95263	0.91579	0.88174	0.66435	2.68834	2.21220
522	1050168	PI3	UP	2120079	EIF2AK2	DOWN	0.83683	0.64921	0.94737	0.88947	0.90261	0.52348	2.68680	2.06216
529	1030100	HS.386275	DOWN	7550066	MERTK	UP	0.91460	0.55873	0.83684	0.85789	0.93217	0.66261	2.68362	2.07923
543	1030100	HS.386275	DOWN	3850647	PTPN20	UP	0.89841	0.49111	0.86316	0.91053	0.91826	0.94087	2.67983	2.34251
22	5090215	IFI6	DOWN	7550066	MERTK	UP	0.92063	0.60349	0.89474	0.78421	0.86087	0.67478	2.67624	2.06249
296	2140707	SLPI	UP	3360615	FCER1A	DOWN	0.83746	0.60571	0.97895	0.88947	0.85913	0.69565	2.67554	2.19084
377	2000148	IFIT1	DOWN	2120079	EIF2AK2	DOWN	0.89365	0.89079	0.86316	0.73158	0.91826	0.94087	2.67507	2.56324
688	150315	C21ORF7	DOWN	2810767	EBI3	UP	0.86825	0.48635	0.91053	0.87895	0.89565	0.61217	2.67443	1.97747
315	2120079	EIF2AK2	DOWN	3850647	PTPN20	UP	0.89556	0.51048	0.85789	0.86842	0.91130	0.91478	2.66475	2.29368
76	3990170	IFI27	DOWN	4480730	HBM	DOWN	0.82127	0.91460	0.90000	0.77895	0.93565	0.77391	2.65692	2.46746
556	1030100	HS.386275	DOWN	2000148	IFIT1	DOWN	0.85683	0.90317	0.87368	0.75263	0.92522	0.94783	2.65573	2.60363
28	5090215	IFI6	DOWN	5550452	KCNMA1	UP	0.92095	0.67302	0.91053	0.76842	0.82087	0.74261	2.65235	2.18405

690	150315	C21ORF7	DOWN	2510356	EMR1	UP	0.83968	0.61048	0.90526	0.85789	0.89739	0.52870	2.64234	1.99707
342	2030309	SERPING1	DOWN	3830735	UPB1	UP	0.88444	0.67492	0.89474	0.71579	0.86261	0.67826	2.64179	2.06897
504	1050168	PI3	UP	5090215	IF16	DOWN	0.84889	0.63429	0.95789	0.88947	0.83478	0.58957	2.64157	2.11332
99	3850647	PTPN20	UP	5090215	IF16	DOWN	0.92159	0.56921	0.91579	0.84211	0.79304	0.80696	2.63042	2.21827
75	3990170	IF127	DOWN	4670327	FBX07	DOWN	0.83746	0.92159	0.88421	0.82105	0.90783	0.85913	2.62950	2.60177
673	150315	C21ORF7	DOWN	5550452	KCNMA1	UP	0.83778	0.53238	0.93684	0.81053	0.85217	0.72348	2.62679	2.06639
326	2030309	SERPING1	DOWN	7550066	MERTK	UP	0.88095	0.68603	0.86842	0.62105	0.87652	0.68348	2.62590	1.99056
479	1090390	OAS1	DOWN	3870338	IF144L	DOWN	0.83079	0.90413	0.94737	0.81579	0.84696	0.95478	2.62512	2.67470
339	2030309	SERPING1	DOWN	3870338	IF144L	DOWN	0.80698	0.88349	0.91053	0.80000	0.90609	0.92696	2.62360	2.61045
664	520408	IFIT3	DOWN	1030100	HS.386275	DOWN	0.79524	0.89175	0.90526	0.73684	0.92174	0.95304	2.62224	2.58163
387	1510424	S100P	UP	4670327	FBX07	DOWN	0.87968	0.72254	0.89474	0.97368	0.84348	0.84696	2.61790	2.54318
668	150315	C21ORF7	DOWN	7400747	FAM89A	UP	0.84571	0.54413	0.86842	0.92632	0.90261	0.64348	2.61674	2.11392
678	150315	C21ORF7	DOWN	4040242	FAM89A	UP	0.84476	0.52825	0.86842	0.92105	0.89739	0.47826	2.61057	1.92757
683	150315	C21ORF7	DOWN	3830735	UPB1	UP	0.82571	0.55556	0.90526	0.94737	0.87652	0.73217	2.60750	2.23510
699	150315	C21ORF7	DOWN	1050168	PI3	UP	0.82889	0.67905	0.91579	0.93684	0.86087	0.61217	2.60555	2.22806
332	2030309	SERPING1	DOWN	5550452	KCNMA1	UP	0.89238	0.71651	0.84737	0.61053	0.85913	0.72174	2.59888	2.04877
516	1050168	PI3	UP	3360615	FCER1A	DOWN	0.84635	0.64444	0.95263	0.85789	0.79304	0.67826	2.59202	2.18060
419	1450358	HBD	DOWN	3990170	IF127	DOWN	0.80952	0.91714	0.86316	0.77895	0.91652	0.77043	2.58920	2.46653
590	1010546	LOC649143	DOWN	1510424	S100P	UP	0.87206	0.74159	0.91053	0.97368	0.80348	0.82783	2.58607	2.54310
198	3360343	RSAD2	DOWN	5090215	IF16	DOWN	0.86889	0.89460	0.85789	0.80526	0.85391	0.95478	2.58070	2.65465
575	1010546	LOC649143	DOWN	3870338	IF144L	DOWN	0.81143	0.91397	0.89474	0.80526	0.86957	0.91652	2.57573	2.63575
359	2000148	IFIT1	DOWN	5090215	IF16	DOWN	0.86889	0.89714	0.81579	0.78421	0.88870	0.94783	2.57337	2.62918
681	150315	C21ORF7	DOWN	3850647	PTPN20	UP	0.85079	0.55873	0.86842	0.91053	0.84348	0.85391	2.56269	2.32317
682	150315	C21ORF7	DOWN	3830762	TMEM119	UP	0.81556	0.52825	0.92632	0.95789	0.81913	0.72000	2.56100	2.20615
166	3780187	GYPB	DOWN	3990170	IF127	DOWN	0.80540	0.89714	0.84737	0.77895	0.90783	0.78957	2.56059	2.46566
628	620544	HLA-DRB6	DOWN	1050168	PI3	UP	0.86000	0.58413	0.89474	0.91579	0.80522	0.61565	2.55995	2.11557
340	2030309	SERPING1	DOWN	3850647	PTPN20	UP	0.88317	0.66667	0.88421	0.71579	0.79130	0.80870	2.55869	2.19115
667	150315	C21ORF7	DOWN	7550066	MERTK	UP	0.84222	0.50762	0.85789	0.83158	0.85739	0.68348	2.55751	2.02268
321	2120079	EIF2AK2	DOWN	3360343	RSAD2	DOWN	0.87714	0.88762	0.82105	0.77895	0.85913	0.95478	2.55733	2.62135
594	1010546	LOC649143	DOWN	1050168	PI3	UP	0.83175	0.66444	0.94737	0.87368	0.77565	0.68174	2.55477	2.21987
185	3360615	FCER1A	DOWN	3870338	IF144L	DOWN	0.81302	0.90889	0.83684	0.82632	0.90261	0.94435	2.55247	2.67955
230	2810767	EBI3	UP	3360615	FCER1A	DOWN	0.79587	0.52603	0.95263	0.75789	0.80174	0.54783	2.55024	1.83175
624	620544	HLA-DRB6	DOWN	1510424	S100P	UP	0.86413	0.58762	0.87368	0.97895	0.81217	0.71652	2.54999	2.28309
378	2000148	IFIT1	DOWN	2030309	SERPING1	DOWN	0.78413	0.88444	0.83158	0.76316	0.93043	0.92522	2.54614	2.57282
533	1030100	HS.386275	DOWN	6510170	IFIT3	DOWN	0.80190	0.89587	0.89474	0.75789	0.84870	0.92174	2.54534	2.57551
586	1010546	LOC649143	DOWN	2140707	SLPI	UP	0.83016	0.62794	0.94737	0.93158	0.76348	0.66087	2.54101	2.22039

88	3870338	IFI44L	DOWN	4480730	HBM	DOWN	0.77651	0.94000	0.85263	0.80526	0.91130	0.86783	2.54044	2.61309
173	3360615	FCER1A	DOWN	7400747	FAM89A	UP	0.79968	0.56921	0.91053	0.81053	0.82957	0.81913	2.53977	2.19886
560	1030100	HS.386275	DOWN	1090390	OAS1	DOWN	0.78127	0.90063	0.86316	0.68421	0.89391	0.94609	2.53834	2.53093
273	2510356	EMR1	UP	3360615	FCER1A	DOWN	0.82349	0.60825	0.92105	0.72105	0.79304	0.68000	2.53759	2.00931
346	2030309	SERPING1	DOWN	3360343	RSAD2	DOWN	0.77651	0.87937	0.81579	0.80526	0.94435	0.92348	2.53665	2.60811
188	3360615	FCER1A	DOWN	3830735	UPB1	UP	0.82032	0.57460	0.94737	0.78947	0.76870	0.54783	2.53638	1.91190
381	1510424	S100P	UP	6980192	HBZ	DOWN	0.84698	0.58508	0.86316	0.86316	0.82609	0.69739	2.53623	2.14563
680	150315	C21ORF7	DOWN	3870338	IFI44L	DOWN	0.80698	0.93619	0.84737	0.85789	0.88000	0.96174	2.53435	2.75582
70	3990170	IFI27	DOWN	6940086	GYPE	DOWN	0.80063	0.89810	0.83158	0.78947	0.90087	0.76348	2.53308	2.45105
323	2120079	EIF2AK2	DOWN	2600747	IFI27	DOWN	0.82762	0.86889	0.84211	0.67368	0.85913	0.94609	2.52885	2.48866
551	1030100	HS.386275	DOWN	2600747	IFI27	DOWN	0.75016	0.88889	0.86316	0.68947	0.91130	0.94957	2.52462	2.52793
388	1510424	S100P	UP	4480730	HBM	DOWN	0.89460	0.64000	0.87895	0.99474	0.74435	0.78435	2.51790	2.41908
486	1090390	OAS1	DOWN	3360343	RSAD2	DOWN	0.78476	0.90476	0.90526	0.81053	0.82783	0.95826	2.51785	2.67355
87	3870338	IFI44L	DOWN	4670327	FBXO7	DOWN	0.80889	0.92794	0.79474	0.87368	0.91130	0.96174	2.51493	2.76336
493	1090390	OAS1	DOWN	2000148	IFI27	DOWN	0.82444	0.90730	0.80000	0.79474	0.89043	0.95652	2.51488	2.65856
74	3990170	IFI27	DOWN	5090215	IFI6	DOWN	0.84825	0.92794	0.84737	0.89474	0.81913	0.89913	2.51475	2.72180
149	3780452	IFIT1L	DOWN	3990170	IFI27	DOWN	0.78794	0.89492	0.84211	0.76316	0.88174	0.75304	2.51178	2.41112
541	1030100	HS.386275	DOWN	3990170	IFI27	DOWN	0.83746	0.93016	0.87368	0.88421	0.79652	0.94609	2.50767	2.76046
183	3360615	FCER1A	DOWN	4040242	FAM89A	UP	0.80730	0.55968	0.91053	0.81579	0.78783	0.69565	2.50565	2.07112
385	1510424	S100P	UP	5550452	KCNMA1	UP	0.74254	0.87492	0.89474	1.00000	0.86435	0.89217	2.50162	2.76709
534	1030100	HS.386275	DOWN	5700725	EPST11	DOWN	0.77365	0.90190	0.91053	0.70000	0.81739	0.94261	2.50157	2.54451
620	620544	HLA-DRB6	DOWN	2140707	SLPI	UP	0.83746	0.50540	0.86842	0.96842	0.79304	0.56348	2.49892	2.03730
420	1450358	HBD	DOWN	3870338	IFI44L	DOWN	0.78381	0.92825	0.82632	0.82105	0.88522	0.85913	2.49534	2.60844
184	3360615	FCER1A	DOWN	3990170	IFI27	DOWN	0.83810	0.93048	0.82105	0.90000	0.83478	0.88870	2.49393	2.71917
285	2140707	SLPI	UP	4670327	FBXO7	DOWN	0.80286	0.66063	0.87895	0.97368	0.81043	0.75130	2.49224	2.38562
379	1510424	S100P	UP	7550066	MERTK	UP	0.71397	0.88286	0.88947	0.98947	0.88696	0.88696	2.49040	2.75929
574	1010546	LOC649143	DOWN	3990170	IFI27	DOWN	0.84254	0.92698	0.83684	0.87368	0.80696	0.87652	2.48634	2.67719
357	2000148	IFIT1	DOWN	5700725	EPST11	DOWN	0.83333	0.89968	0.77368	0.78421	0.87826	0.94957	2.48528	2.63346
679	150315	C21ORF7	DOWN	3990170	IFI27	DOWN	0.82540	0.94952	0.87368	0.88947	0.78609	0.93043	2.48517	2.76943
589	1010546	LOC649143	DOWN	2000148	IFIT1	DOWN	0.80444	0.90825	0.81053	0.74211	0.86957	0.91304	2.48454	2.56340
199	3360343	RSAD2	DOWN	4670327	FBXO7	DOWN	0.79333	0.91270	0.77368	0.77895	0.91652	0.92000	2.48354	2.61165
694	150315	C21ORF7	DOWN	2000148	IFIT1	DOWN	0.79683	0.92762	0.76842	0.81053	0.91652	0.93913	2.48177	2.67728
200	3360343	RSAD2	DOWN	4480730	HBM	DOWN	0.75492	0.92984	0.84211	0.70526	0.88000	0.85565	2.47703	2.49076
656	520408	IFIT3	DOWN	2120079	EIF2AK2	DOWN	0.84159	0.86921	0.89474	0.73158	0.72348	0.94957	2.45980	2.55035
69	3990170	IFI27	DOWN	6980192	HBZ	DOWN	0.76349	0.88413	0.86316	0.81053	0.82957	0.83130	2.45622	2.52596
371	2000148	IFIT1	DOWN	3360615	FCER1A	DOWN	0.80317	0.90317	0.75789	0.77368	0.89391	0.94435	2.45498	2.62121

286	2140707	SLPI	UP	4480730	HBM	DOWN	0.84032	0.56000	0.88421	0.97368	0.73043	0.69391	2.45496	2.22760
187	3360615	FCER1A	DOWN	3830762	TMEM119	UP	0.77079	0.53460	0.95789	0.79474	0.72348	0.57043	2.45217	1.89977
435	1450358	HBD	DOWN	1510424	S100P	UP	0.85937	0.67810	0.84737	0.95789	0.74435	0.76348	2.45108	2.39947
397	1510424	S100P	UP	3780187	GYPB	DOWN	0.85683	0.61619	0.83158	0.90000	0.76174	0.78087	2.45014	2.29706
313	2120079	EIF2AK2	DOWN	3990170	IF127	DOWN	0.84857	0.92984	0.85263	0.91053	0.74793	0.95826	2.44903	2.79863
360	2000148	IFIT1	DOWN	4670327	FBXO7	DOWN	0.80381	0.92222	0.73158	0.78421	0.91304	0.95826	2.44843	2.66469
195	3360343	RSAD2	DOWN	6510170	IFIT3	DOWN	0.77365	0.89143	0.76316	0.82105	0.90957	0.94957	2.44637	2.66205
505	1050168	PI3	UP	4670327	FBXO7	DOWN	0.79460	0.68857	0.85789	0.95263	0.79130	0.73043	2.44380	2.37164
506	1050168	PI3	UP	4480730	HBM	DOWN	0.82540	0.64508	0.89474	0.94211	0.72348	0.71304	2.44361	2.30023
582	1010546	LOC649143	DOWN	3360343	RSAD2	DOWN	0.78032	0.90857	0.79474	0.77895	0.86783	0.89913	2.44288	2.58665
687	150315	C21ORF7	DOWN	3360343	RSAD2	DOWN	0.77683	0.92857	0.77895	0.83684	0.88696	0.96000	2.44273	2.72541
361	2000148	IFIT1	DOWN	4480730	HBM	DOWN	0.76381	0.93651	0.78421	0.73684	0.88522	0.88000	2.43324	2.55335
559	1030100	HS.386275	DOWN	1440615	OTOF	DOWN	0.78889	0.89905	0.78421	0.62632	0.85913	0.94783	2.43223	2.47319
583	1010546	LOC649143	DOWN	2810767	EBI3	UP	0.81619	0.51619	0.90526	0.82632	0.70957	0.56000	2.43102	1.90251
77	3990170	IF127	DOWN	4150600	EIF1AY	DOWN	0.77079	0.92190	0.84211	0.75789	0.81565	0.82783	2.42855	2.50763
172	3360615	FCER1A	DOWN	7550066	MERTK	UP	0.80857	0.48857	0.86316	0.80000	0.75304	0.48696	2.42477	1.77553
210	3360343	RSAD2	DOWN	3360615	FCER1A	DOWN	0.78571	0.90540	0.74737	0.82632	0.88870	0.94087	2.42178	2.67258
585	1010546	LOC649143	DOWN	2510356	EMR1	UP	0.83143	0.59746	0.87368	0.81053	0.71652	0.60522	2.42163	2.01320
608	620544	HLA-DRB6	DOWN	3990170	IF127	DOWN	0.76349	0.92159	0.86842	0.83158	0.78957	0.86087	2.42148	2.61404
389	1510424	S100P	UP	4150600	EIF1AY	DOWN	0.84000	0.62603	0.81579	0.94211	0.76174	0.80000	2.41753	2.36814
563	1010546	LOC649143	DOWN	7400747	FAM89A	UP	0.81683	0.57270	0.82632	0.86842	0.77391	0.72696	2.41705	2.16808
83	3870338	IFI44L	DOWN	6510170	IFIT3	DOWN	0.77873	0.89746	0.77368	0.82105	0.86435	0.94435	2.41676	2.66286
186	3360615	FCER1A	DOWN	3850647	PTPN20	UP	0.79556	0.58190	0.88947	0.77368	0.73043	0.74087	2.41546	2.09646
434	1450358	HBD	DOWN	2000148	IFIT1	DOWN	0.77556	0.91905	0.77895	0.74211	0.85913	0.87130	2.41363	2.53246
382	1510424	S100P	UP	6940086	GYPE	DOWN	0.85429	0.61079	0.84211	0.90000	0.71652	0.77043	2.41291	2.28123
178	3360615	FCER1A	DOWN	5550452	KCNMA1	UP	0.78540	0.49714	0.86842	0.81053	0.75652	0.56870	2.41034	1.87636
279	2140707	SLPI	UP	6980192	HBZ	DOWN	0.80603	0.48000	0.82632	0.88421	0.77217	0.63652	2.40452	2.00073
499	1050168	PI3	UP	6980192	HBZ	DOWN	0.80032	0.58667	0.82632	0.91053	0.77565	0.62609	2.40229	2.12328
396	1510424	S100P	UP	3780452	IFIT1L	DOWN	0.84190	0.60921	0.81579	0.85789	0.74261	0.75652	2.40030	2.22362
89	3870338	IFI44L	DOWN	4150600	EIF1AY	DOWN	0.73302	0.92032	0.78947	0.70526	0.87652	0.86087	2.39901	2.48645
245	2600747	IFIT2	DOWN	3870338	IFI44L	DOWN	0.79873	0.90540	0.87895	0.83158	0.72000	0.95478	2.39768	2.69176
427	1450358	HBD	DOWN	3360343	RSAD2	DOWN	0.75651	0.91873	0.81053	0.71053	0.82783	0.81391	2.39486	2.44317
578	1010546	LOC649143	DOWN	3830735	UPB1	UP	0.82857	0.58032	0.89474	0.85789	0.65565	0.53739	2.37896	1.97560
196	3360343	RSAD2	DOWN	5700725	EPST1L	DOWN	0.78635	0.89746	0.78421	0.81579	0.80522	0.94435	2.37578	2.65760
167	3780187	GYPB	DOWN	3870338	IFI44L	DOWN	0.75111	0.92063	0.74211	0.83158	0.88174	0.89739	2.37496	2.64961
639	520408	IFIT3	DOWN	4670327	FBXO7	DOWN	0.75841	0.88571	0.74211	0.66842	0.87304	0.90609	2.37356	2.46022

390	1510424	S100P	UP	4040242	FAM89A	UP	0.71873	0.89238	0.84737	0.98947	0.80174	0.89565	2.36784	2.77751
393	1510424	S100P	UP	3850647	PTPN20	UP	0.69048	0.87143	0.77895	0.98947	0.89739	0.89739	2.36681	2.75829
597	620544	HLA-DRB6	DOWN	7400747	FAM89A	UP	0.82159	0.55651	0.76316	0.85263	0.78087	0.65043	2.36561	2.05957
507	1050168	PI3	UP	4150600	EIF1AY	DOWN	0.79810	0.62635	0.87368	0.87895	0.69043	0.65739	2.36221	2.16269
82	3870338	IFI44L	DOWN	6940086	GYPE	DOWN	0.75397	0.92190	0.74211	0.83158	0.86609	0.85565	2.36216	2.60914
356	2000148	IFIT1	DOWN	6510170	IFIT3	DOWN	0.77556	0.89397	0.68947	0.80000	0.89391	0.93739	2.35894	2.63136
619	620544	HLA-DRB6	DOWN	2510356	EMR1	UP	0.85238	0.51651	0.75263	0.83158	0.75304	0.52696	2.35806	1.87504
262	2510356	EMR1	UP	4670327	FBXO7	DOWN	0.81333	0.62222	0.80526	0.82105	0.73913	0.74087	2.35773	2.18414
362	2000148	IFIT1	DOWN	4150600	EIF1AY	DOWN	0.72413	0.90159	0.74211	0.67368	0.89043	0.85739	2.35667	2.43266
644	520408	IFIT3	DOWN	3870338	IFI44L	DOWN	0.77683	0.90571	0.80526	0.83158	0.77391	0.96870	2.35600	2.70599
263	2510356	EMR1	UP	4480730	HBM	DOWN	0.85778	0.52889	0.85789	0.83684	0.63652	0.65739	2.35219	2.02312
395	1510424	S100P	UP	3830735	UPB1	UP	0.69587	0.87873	0.78947	0.99474	0.86609	0.89913	2.35143	2.77260
33	4670327	FBXO7	DOWN	6510170	IFIT3	DOWN	0.75778	0.89270	0.76842	0.67895	0.82261	0.86435	2.34881	2.43599
287	2140707	SLPI	UP	4150600	EIF1AY	DOWN	0.78794	0.55238	0.83158	0.91053	0.72870	0.65565	2.34821	2.11856
240	2600747	IFIT2	DOWN	4670327	FBXO7	DOWN	0.73937	0.89841	0.71053	0.69474	0.89739	0.94609	2.34728	2.53924
638	520408	IFIT3	DOWN	5090215	IFI6	DOWN	0.76730	0.88921	0.82632	0.78421	0.75304	0.92870	2.34666	2.60211
665	520408	IFIT3	DOWN	1010546	LOC649143	DOWN	0.73111	0.89175	0.78421	0.66842	0.83130	0.84000	2.34663	2.40017
449	1440615	OTOF	DOWN	3870338	IFI44L	DOWN	0.72286	0.90159	0.85263	0.80526	0.76870	0.95826	2.34418	2.66511
526	1050168	PI3	UP	1450358	HBD	DOWN	0.79492	0.67397	0.85263	0.95263	0.69217	0.68522	2.33973	2.31182
617	620544	HLA-DRB6	DOWN	2810767	EBI3	UP	0.82063	0.58540	0.77368	0.82105	0.74261	0.49043	2.33693	1.89688
306	2120079	EIF2AK2	DOWN	5700725	EPST11	DOWN	0.82667	0.88286	0.87895	0.70526	0.63130	0.92348	2.33692	2.51160
573	1010546	LOC649143	DOWN	4040242	FAM89A	UP	0.81683	0.56127	0.80526	0.86316	0.71478	0.63304	2.33687	2.05747
612	620544	HLA-DRB6	DOWN	3830735	UPB1	UP	0.84317	0.53016	0.78947	0.85263	0.70261	0.55652	2.33526	1.93931
256	2510356	EMR1	UP	6980192	HBZ	DOWN	0.79238	0.52317	0.77895	0.74737	0.76174	0.60000	2.33307	1.87054
611	620544	HLA-DRB6	DOWN	3830762	TMEM119	UP	0.80063	0.56254	0.84737	0.91053	0.68348	0.58609	2.33148	2.05915
431	1450358	HBD	DOWN	2140707	SLPI	UP	0.79016	0.61333	0.84211	0.97368	0.69739	0.65217	2.32966	2.23919
515	1050168	PI3	UP	3780187	GYPB	DOWN	0.79238	0.63810	0.84211	0.90000	0.69391	0.70783	2.32840	2.24592
577	1010546	LOC649143	DOWN	3830762	TMEM119	UP	0.76825	0.54127	0.93158	0.87368	0.62435	0.52696	2.32418	1.94191
239	2600747	IFIT2	DOWN	5090215	IFI6	DOWN	0.74698	0.88730	0.73158	0.77895	0.84522	0.94261	2.32378	2.60886
30	4670327	FBXO7	DOWN	7400747	FAM89A	UP	0.79937	0.60159	0.74211	0.89474	0.78087	0.81391	2.32234	2.31024
609	620544	HLA-DRB6	DOWN	3870338	IFI44L	DOWN	0.72921	0.90952	0.78947	0.80526	0.80348	0.93217	2.32216	2.64696
294	2140707	SLPI	UP	3780452	IFIT1L	DOWN	0.78794	0.55079	0.82105	0.88947	0.70783	0.63652	2.31682	2.07679
478	1090390	OAS1	DOWN	3990170	IFIT2	DOWN	0.77873	0.92825	0.83158	0.88947	0.70087	0.95826	2.31118	2.77599
607	620544	HLA-DRB6	DOWN	4040242	FAM89A	UP	0.82254	0.56444	0.75263	0.83684	0.73565	0.54261	2.31082	1.94390
584	1010546	LOC649143	DOWN	2600747	IFIT2	DOWN	0.72571	0.88476	0.73684	0.62632	0.84348	0.89565	2.30603	2.40673
338	2030309	SERPING1	DOWN	3990170	IFI27	DOWN	0.75016	0.91365	0.77895	0.88947	0.77565	0.92000	2.30476	2.72312

295	2140707	SLPI	UP	3780187	GYPB	DOWN	0.79016	0.56635	0.81053	0.92105	0.70261	0.70087	2.30329	2.18827
689	150315	C21ORF7	DOWN	2600747	IFIT2	DOWN	0.71810	0.91651	0.69474	0.75789	0.89043	0.93913	2.30327	2.61353
500	1050168	PI3	UP	6940086	GYPE	DOWN	0.79302	0.64032	0.84211	0.91053	0.66435	0.69391	2.29947	2.24476
209	3360343	RSAD2	DOWN	3780187	GYPB	DOWN	0.72095	0.90825	0.72632	0.73684	0.85217	0.84522	2.29944	2.49031
514	1050168	PI3	UP	3780452	IFIT1L	DOWN	0.78190	0.62317	0.82632	0.90000	0.69043	0.64522	2.29866	2.16839
201	3360343	RSAD2	DOWN	4150600	EIF1AY	DOWN	0.70889	0.90413	0.73158	0.67895	0.85739	0.82261	2.29786	2.40568
38	4480730	HBM	DOWN	7400747	FAM89A	UP	0.85365	0.51333	0.73158	0.90526	0.70957	0.75826	2.29479	2.17686
491	1090390	OAS1	DOWN	2120079	EIF2AK2	DOWN	0.83206	0.89143	0.80000	0.69474	0.66261	0.94435	2.29467	2.53051
355	2000148	IFIT1	DOWN	6940086	GYPE	DOWN	0.73302	0.91937	0.71053	0.74211	0.85043	0.83478	2.29398	2.49625
150	3780452	IFIT1L	DOWN	3870338	IF144L	DOWN	0.72381	0.91873	0.72632	0.83158	0.84348	0.86609	2.29360	2.61640
34	4670327	FBXO7	DOWN	5700725	EPST11	DOWN	0.73968	0.92476	0.70000	0.64737	0.85043	0.90957	2.29012	2.48170
280	2140707	SLPI	UP	6940086	GYPE	DOWN	0.79302	0.56508	0.82632	0.91579	0.66957	0.66957	2.28890	2.15043
370	2000148	IFIT1	DOWN	3780187	GYPB	DOWN	0.73460	0.91778	0.68947	0.74211	0.86435	0.88348	2.28842	2.54336
3	6980192	HBZ	DOWN	7400747	FAM89A	UP	0.77333	0.53873	0.73684	0.77895	0.77565	0.66087	2.28583	1.97855
400	1510424	S100P	UP	2810767	EBI3	UP	0.70127	0.91238	0.78947	1.00000	0.79478	0.90783	2.28553	2.82021
194	3360343	RSAD2	DOWN	6940086	GYPE	DOWN	0.72127	0.91048	0.72105	0.74211	0.84174	0.79478	2.28406	2.44736
658	520408	IFIT3	DOWN	2000148	IFIT1	DOWN	0.77429	0.89587	0.70000	0.81053	0.80870	0.96870	2.28298	2.67509
463	1440615	OTOF	DOWN	2000148	IFIT1	DOWN	0.69302	0.90540	0.76842	0.75789	0.81913	0.95652	2.28057	2.61981
640	520408	IFIT3	DOWN	4480730	HBM	DOWN	0.70508	0.91683	0.77368	0.61053	0.80174	0.82783	2.28050	2.35518
241	2600747	IFIT2	DOWN	4480730	HBM	DOWN	0.69175	0.91714	0.73684	0.63684	0.85043	0.87130	2.27902	2.42529
602	620544	HLA-DRB6	DOWN	5550452	KCNMA1	UP	0.81143	0.58921	0.77895	0.77895	0.68522	0.41043	2.27559	1.77859
129	3830735	UPB1	UP	4670327	FBXO7	DOWN	0.79016	0.60413	0.79474	0.92632	0.69043	0.65391	2.27533	2.18436
474	1090390	OAS1	DOWN	4670327	FBXO7	DOWN	0.73841	0.92413	0.67895	0.58421	0.85565	0.89739	2.27301	2.40573
660	520408	IFIT3	DOWN	1450358	HBD	DOWN	0.72698	0.89333	0.77368	0.63158	0.77217	0.78435	2.27284	2.30926
72	3990170	IFIT2	DOWN	5700725	EPST11	DOWN	0.78571	0.93238	0.77895	0.90526	0.70609	0.95652	2.27075	2.79417
64	4040242	FAM89A	UP	4670327	FBXO7	DOWN	0.80952	0.59492	0.72632	0.88421	0.73391	0.75478	2.26975	2.23391
283	2140707	SLPI	UP	5550452	KCNMA1	UP	0.62794	0.82984	0.85789	1.00000	0.78087	0.88870	2.26670	2.71854
610	620544	HLA-DRB6	DOWN	3850647	PTPN20	UP	0.82159	0.53492	0.79474	0.82105	0.64870	0.65043	2.26502	2.00641
41	4480730	HBM	DOWN	6510170	IFIT3	DOWN	0.72413	0.92286	0.79474	0.65789	0.74609	0.76870	2.26495	2.34945
562	1010546	LOC649143	DOWN	7550066	MERTK	UP	0.82095	0.54222	0.81053	0.80526	0.63130	0.51826	2.26278	1.86575
81	3870338	IF144L	DOWN	6980192	HBZ	DOWN	0.72349	0.91810	0.73684	0.81579	0.80174	0.90783	2.26207	2.64171
291	2140707	SLPI	UP	3850647	PTPN20	UP	0.55968	0.84698	0.82105	0.97895	0.88000	0.85217	2.26074	2.67811
155	3780187	GYPB	DOWN	7400747	FAM89A	UP	0.79429	0.48508	0.74737	0.76842	0.71826	0.74609	2.25992	1.99959
703	150315	C21ORF7	DOWN	520408	IFIT3	DOWN	0.72063	0.92159	0.74211	0.79474	0.79478	0.95826	2.25752	2.67459
429	1450358	HBD	DOWN	2600747	IFIT2	DOWN	0.70794	0.89270	0.74211	0.61053	0.80348	0.84348	2.25352	2.34670
567	1010546	LOC649143	DOWN	5700725	EPST11	DOWN	0.71429	0.89841	0.77368	0.65263	0.76174	0.83130	2.24971	2.38235

475	1090390	OA51	DOWN	4480730	HBM	DOWN	0.70349	0.92730	0.75263	0.52105	0.79130	0.80000	2.24743	2.24835
566	1010546	LOC649143	DOWN	6510170	IFIT3	DOWN	0.73270	0.89365	0.76316	0.71053	0.75130	0.79304	2.24716	2.39722
623	620544	HLA-DRB6	DOWN	2000148	IFIT1	DOWN	0.71492	0.90857	0.72632	0.77368	0.80522	0.93391	2.24645	2.61617
220	2810767	EBI3	UP	4480730	HBM	DOWN	0.87365	0.56381	0.72105	0.88421	0.64870	0.42087	2.24340	1.86889
374	2000148	IFIT1	DOWN	2600747	IFIT2	DOWN	0.81206	0.89746	0.78947	0.78421	0.64174	0.94261	2.24328	2.62428
65	4040242	FAM89A	UP	4480730	HBM	DOWN	0.85556	0.52095	0.75263	0.90000	0.63478	0.66957	2.24297	2.09052
58	4040242	FAM89A	UP	6980192	HBZ	DOWN	0.77365	0.54127	0.73684	0.75789	0.73043	0.59826	2.24093	1.89743
123	3830735	UPB1	UP	6980192	HBZ	DOWN	0.79175	0.52444	0.76842	0.79474	0.68000	0.52870	2.24017	1.84788
130	3830735	UPB1	UP	4480730	HBM	DOWN	0.84095	0.51683	0.79474	0.93158	0.60174	0.57217	2.23743	2.02058
219	2810767	EBI3	UP	4670327	FBXO7	DOWN	0.81365	0.56413	0.71579	0.88421	0.70783	0.67304	2.23727	2.12138
42	4480730	HBM	DOWN	5700725	EPSTI1	DOWN	0.71429	0.92730	0.74211	0.58947	0.77739	0.78783	2.23378	2.30460
651	520408	IFIT3	DOWN	3360343	RSAD2	DOWN	0.77524	0.89746	0.71579	0.83158	0.74261	0.96348	2.23364	2.69252
27	5090215	IFI6	DOWN	5700725	EPSTI1	DOWN	0.81492	0.89206	0.72632	0.78421	0.69217	0.90087	2.23341	2.57714
26	5090215	IFI6	DOWN	6510170	IFIT3	DOWN	0.78952	0.88571	0.79474	0.78421	0.64870	0.91130	2.23296	2.58123
5	6940086	GYPE	DOWN	7400747	FAM89A	UP	0.79429	0.49333	0.74737	0.76842	0.69043	0.72174	2.23209	1.98349
272	2510356	EMR1	UP	3780187	GYPB	DOWN	0.79302	0.51683	0.73684	0.71053	0.69739	0.70435	2.22725	1.93170
503	1050168	PI3	UP	5550452	KCNMA1	UP	0.65651	0.83048	0.82105	0.98947	0.74957	0.80522	2.22713	2.62517
448	1440615	OTOF	DOWN	3990170	IFI27	DOWN	0.72381	0.90730	0.82632	0.89474	0.67652	0.96348	2.22665	2.76552
411	1450358	HBD	DOWN	6510170	IFIT3	DOWN	0.72921	0.90540	0.80000	0.67895	0.69565	0.74609	2.22486	2.33043
47	4150600	EIF1AY	DOWN	7400747	FAM89A	UP	0.77016	0.47651	0.72105	0.78947	0.73217	0.73565	2.22339	2.00163
208	3360343	RSAD2	DOWN	3780452	IFIT1L	DOWN	0.69968	0.90095	0.71053	0.75789	0.81043	0.81565	2.22064	2.47450
596	620544	HLA-DRB6	DOWN	7550066	MERTK	UP	0.81937	0.56413	0.70526	0.83684	0.69565	0.54957	2.22028	1.95053
108	3830762	TMEM119	UP	6980192	HBZ	DOWN	0.74825	0.53175	0.82105	0.86316	0.65043	0.48174	2.21974	1.87664
165	3780187	GYPB	DOWN	4040242	FAM89A	UP	0.79460	0.49873	0.73684	0.76316	0.68522	0.69043	2.21666	1.95232
354	2000148	IFIT1	DOWN	6980192	HBZ	DOWN	0.70000	0.90540	0.72105	0.71053	0.79478	0.90261	2.21584	2.51853
305	2120079	EIF2AK2	DOWN	6510170	IFIT3	DOWN	0.83556	0.87397	0.81053	0.77368	0.56870	0.93217	2.21478	2.57983
369	2000148	IFIT1	DOWN	3780452	IFIT1L	DOWN	0.70444	0.90825	0.68421	0.75263	0.82609	0.86435	2.21474	2.52523
576	1010546	LOC649143	DOWN	3850647	PTPN20	UP	0.80952	0.57492	0.83684	0.84211	0.56696	0.58261	2.21332	1.99963
593	1010546	LOC649143	DOWN	1090390	OAS1	DOWN	0.71714	0.88921	0.71053	0.61053	0.78435	0.83652	2.21202	2.33625
221	2810767	EBI3	UP	4150600	EIF1AY	DOWN	0.78381	0.49016	0.74211	0.75263	0.68174	0.61913	2.20765	1.86192
445	1440615	OTOF	DOWN	4480730	HBM	DOWN	0.70825	0.93238	0.72632	0.52105	0.77217	0.85565	2.20674	2.30909
568	1010546	LOC649143	DOWN	5550452	KCNMA1	UP	0.78730	0.48159	0.77368	0.87895	0.64522	0.48348	2.20620	1.84401
251	2600747	IFIT2	DOWN	3360615	FCER1A	DOWN	0.71683	0.88508	0.61579	0.77368	0.87304	0.92000	2.20566	2.57876
444	1440615	OTOF	DOWN	4670327	FBXO7	DOWN	0.73683	0.93333	0.64737	0.55789	0.81913	0.92870	2.20332	2.41992
592	1010546	LOC649143	DOWN	1440615	OTOF	DOWN	0.73492	0.88381	0.66842	0.62105	0.79826	0.85043	2.20160	2.35530
138	3780452	IFIT1L	DOWN	7400747	FAM89A	UP	0.77556	0.50444	0.72632	0.77368	0.69913	0.70609	2.20100	1.98422

513	1050168	PI3	UP	3830735	UPB1	UP	0.66095	0.82127	0.83158	0.98421	0.70783	0.85565	2.20036	2.66113
271	2510356	EMR1	UP	3780452	IFIT1L	DOWN	0.78317	0.49778	0.72632	0.68947	0.69043	0.61913	2.19993	1.80638
114	3830762	TMEM119	UP	4670327	FBXO7	DOWN	0.73778	0.58825	0.82632	0.96316	0.63478	0.57913	2.19888	2.13054
380	1510424	S100P	UP	7400747	FAM89A	UP	0.70222	0.89397	0.84737	0.98947	0.64870	0.91304	2.19829	2.79649
71	3990170	IF127	DOWN	6510170	IFIT3	DOWN	0.72000	0.92825	0.77895	0.91053	0.69913	0.96348	2.19808	2.80226
497	1050168	PI3	UP	7550066	MERTK	UP	0.65778	0.82889	0.83684	0.98421	0.70261	0.83826	2.19723	2.65136
456	1440615	OTOF	DOWN	3360343	RSAD2	DOWN	0.66349	0.90127	0.78421	0.77895	0.74783	0.96348	2.19553	2.64370
257	2510356	EMR1	UP	6940086	GYPE	DOWN	0.79143	0.51333	0.73158	0.71053	0.67130	0.66783	2.19431	1.89169
402	1510424	S100P	UP	2510356	EMR1	UP	0.65841	0.88349	0.77368	1.00000	0.76000	0.89739	2.19210	2.78088
495	1090390	OAS1	DOWN	1450358	HBD	DOWN	0.70698	0.90286	0.75789	0.52105	0.72522	0.76522	2.19010	2.18913
671	150315	C21ORF7	DOWN	6510170	IFIT3	DOWN	0.73270	0.91905	0.73684	0.80526	0.71826	0.93217	2.18780	2.65648
59	4040242	FAM89A	UP	6940086	GYPE	DOWN	0.79429	0.50222	0.73158	0.76842	0.66087	0.64870	2.18673	1.91934
151	3780452	IFIT1L	DOWN	3850647	PTPN20	UP	0.81270	0.48349	0.80526	0.71579	0.56870	0.59478	2.18666	1.79406
511	1050168	PI3	UP	3850647	PTPN20	UP	0.61873	0.85111	0.76842	0.95789	0.79826	0.80348	2.18541	2.61248
412	1450358	HBD	DOWN	5700725	EPST1L	DOWN	0.71524	0.89968	0.76842	0.58947	0.70087	0.76174	2.18453	2.25090
213	2810767	EBI3	UP	6980192	HBZ	DOWN	0.76603	0.56984	0.71579	0.76842	0.70261	0.57391	2.18443	1.91218
616	620544	HLA-DRB6	DOWN	3360343	RSAD2	DOWN	0.69079	0.90159	0.73158	0.79474	0.76174	0.92000	2.18411	2.61632
229	2810767	EBI3	UP	3780187	GYPB	DOWN	0.78476	0.52667	0.70526	0.73684	0.69391	0.59304	2.18394	1.85655
170	3780187	GYPB	DOWN	3830735	UPB1	UP	0.77905	0.49238	0.74211	0.79474	0.66261	0.59826	2.18376	1.88538
168	3780187	GYPB	DOWN	3850647	PTPN20	UP	0.83175	0.53079	0.78421	0.73684	0.56522	0.57391	2.18117	1.84155
650	520408	IFIT3	DOWN	3360615	FCER1A	DOWN	0.71937	0.89333	0.64737	0.79474	0.81391	0.92174	2.18065	2.60981
264	2510356	EMR1	UP	4150600	EIF1AY	DOWN	0.77619	0.46698	0.71579	0.75263	0.68522	0.66261	2.17720	1.88222
641	520408	IFIT3	DOWN	4150600	EIF1AY	DOWN	0.65048	0.87302	0.70000	0.61579	0.82261	0.79652	2.17308	2.28533
193	3360343	RSAD2	DOWN	6980192	HBZ	DOWN	0.67683	0.90000	0.72105	0.70000	0.77217	0.90087	2.17005	2.50087
35	4670327	FBXO7	DOWN	5550452	KCNMA1	UP	0.76635	0.57016	0.74737	0.82632	0.65565	0.60174	2.16937	1.99821
95	3850647	PTPN20	UP	6940086	GYPE	DOWN	0.83270	0.47079	0.79474	0.73684	0.54087	0.56348	2.16830	1.77111
465	1440615	OTOF	DOWN	1450358	HBD	DOWN	0.70000	0.92952	0.72632	0.53158	0.74087	0.80696	2.16719	2.26806
512	1050168	PI3	UP	3830762	TMEM119	UP	0.67048	0.81683	0.72105	0.96842	0.77565	0.78957	2.16718	2.57481
115	3830762	TMEM119	UP	4480730	HBM	DOWN	0.78730	0.51587	0.82105	0.95789	0.55826	0.54957	2.16662	2.02333
116	3830762	TMEM119	UP	4150600	EIF1AY	DOWN	0.74190	0.50698	0.83158	0.82105	0.59304	0.53739	2.16653	1.86543
29	4670327	FBXO7	DOWN	7550066	MERTK	UP	0.78254	0.57365	0.71579	0.81053	0.66609	0.63130	2.16442	2.01548
277	2140707	SLPI	UP	7550066	MERTK	UP	0.58762	0.85365	0.86316	0.99474	0.71304	0.87652	2.16382	2.72491
124	3830735	UPB1	UP	6940086	GYPE	DOWN	0.77810	0.48984	0.74737	0.80000	0.63826	0.56522	2.16372	1.85506
101	3850647	PTPN20	UP	4480730	HBM	DOWN	0.87175	0.50667	0.76842	0.89474	0.52348	0.51478	2.16365	1.91619
461	1440615	OTOF	DOWN	2120079	EIF2AK2	DOWN	0.80603	0.88730	0.70000	0.64211	0.65565	0.93217	2.16168	2.46158
148	3780452	IFIT1L	DOWN	4040242	FAM89A	UP	0.77524	0.50571	0.70526	0.75263	0.68000	0.63478	2.16050	1.89313

214	2810767	EBI3	UP	6940086	GYPE	DOWN	0.78349	0.53206	0.71053	0.73158	0.66435	0.57391	2.15837	1.83756
228	2810767	EBI3	UP	3780452	IFIT1L	DOWN	0.76921	0.54222	0.70000	0.75789	0.68696	0.44000	2.15616	1.74012
662	520408	IFIT3	DOWN	1090390	OAS1	DOWN	0.65206	0.89937	0.80526	0.80526	0.69739	0.94957	2.15472	2.65419
2	6980192	HBZ	DOWN	7550066	MERTK	UP	0.77270	0.55873	0.71579	0.76316	0.66609	0.52870	2.15457	1.85058
66	4040242	FAM89A	UP	4150600	EIF1AY	DOWN	0.76857	0.47841	0.70000	0.78421	0.68522	0.67304	2.15379	1.93567
18	5550452	KCNMA1	UP	6980192	HBZ	DOWN	0.75810	0.56825	0.73684	0.73158	0.65739	0.51826	2.15233	1.81809
169	3780187	GYPB	DOWN	3830762	TMEM119	UP	0.73683	0.50952	0.81053	0.87368	0.60000	0.58783	2.14735	1.97103
153	3780452	IFIT1L	DOWN	3830735	UPB1	UP	0.76762	0.50286	0.71579	0.77895	0.66261	0.48522	2.14602	1.76702
473	1090390	OAS1	DOWN	5090215	IFI6	DOWN	0.75556	0.90127	0.68947	0.77895	0.70087	0.91826	2.14590	2.59848
242	2600747	IFIT2	DOWN	4150600	EIF1AY	DOWN	0.63270	0.86571	0.66842	0.59474	0.84000	0.84174	2.14112	2.30219
109	3830762	TMEM119	UP	6940086	GYPE	DOWN	0.73714	0.49238	0.81053	0.86316	0.59130	0.54261	2.13897	1.89815
176	3360615	FCER1A	DOWN	6510170	IFIT3	DOWN	0.73492	0.89397	0.65789	0.80000	0.74609	0.89391	2.13890	2.58788
100	3850647	PTPN20	UP	4670327	FBXO7	DOWN	0.83524	0.60635	0.77368	0.85263	0.52870	0.56174	2.13762	2.02072
154	3780187	GYPB	DOWN	7550066	MERTK	UP	0.76571	0.51206	0.72105	0.73684	0.65043	0.59130	2.13720	1.84021
643	520408	IFIT3	DOWN	3990170	IFIT2	DOWN	0.73048	0.92730	0.75789	0.92105	0.64870	0.95652	2.13707	2.80488
408	1450358	HBD	DOWN	7400747	FAM89A	UP	0.78286	0.55524	0.66842	0.94211	0.68174	0.71652	2.13302	2.21387
394	1510424	S100P	UP	3830762	TMEM119	UP	0.68286	0.87619	0.58421	1.00000	0.86261	0.87826	2.12968	2.75445
94	3850647	PTPN20	UP	6980192	HBZ	DOWN	0.79587	0.51016	0.75789	0.76842	0.57565	0.61913	2.12942	1.89771
152	3780452	IFIT1L	DOWN	3830762	TMEM119	UP	0.73048	0.50571	0.78421	0.83684	0.61391	0.51130	2.12860	1.85386
160	3780187	GYPB	DOWN	5550452	KCNMA1	UP	0.74825	0.51651	0.73158	0.66842	0.64870	0.56000	2.12853	1.74493
1	7400747	FAM89A	UP	7550066	MERTK	UP	0.56222	0.83016	0.67895	0.97368	0.88696	0.82609	2.12813	2.62993
293	2140707	SLPI	UP	3830735	UPB1	UP	0.58508	0.83587	0.83158	1.00000	0.70783	0.90087	2.12448	2.73674
697	150315	C21ORF7	DOWN	1440615	OTOF	DOWN	0.71746	0.93016	0.63684	0.71579	0.76870	0.95478	2.12300	2.60073
50	4150600	EIF1AY	DOWN	6510170	IFIT3	DOWN	0.66381	0.88032	0.71053	0.66316	0.74609	0.74087	2.12042	2.28434
672	150315	C21ORF7	DOWN	5700725	EPST1L	DOWN	0.71651	0.93683	0.66842	0.77895	0.73391	0.93739	2.11884	2.65316
698	150315	C21ORF7	DOWN	1090390	OAS1	DOWN	0.71778	0.94762	0.63684	0.74737	0.76348	0.95304	2.11810	2.64803
131	3830735	UPB1	UP	4150600	EIF1AY	DOWN	0.76825	0.49492	0.72105	0.78947	0.62783	0.42261	2.11713	1.70700
177	3360615	FCER1A	DOWN	5700725	EPST1L	DOWN	0.71175	0.89746	0.61579	0.74737	0.78783	0.89565	2.11536	2.54048
334	2030309	SERPING1	DOWN	4670327	FBXO7	DOWN	0.72190	0.87937	0.65789	0.61053	0.73043	0.76696	2.11023	2.25685
470	1090390	OAS1	DOWN	6510170	IFIT3	DOWN	0.67143	0.89619	0.77895	0.79474	0.65913	0.93043	2.10951	2.62136
649	520408	IFIT3	DOWN	3780187	GYPB	DOWN	0.66921	0.90000	0.62632	0.69474	0.81043	0.83304	2.10596	2.42778
17	5550452	KCNMA1	UP	7400747	FAM89A	UP	0.60603	0.83968	0.66316	0.99474	0.83304	0.89217	2.10223	2.72659
657	520408	IFIT3	DOWN	2030309	SERPING1	DOWN	0.57238	0.87238	0.64211	0.76316	0.88696	0.91130	2.10144	2.54684
236	2600747	IFIT2	DOWN	6510170	IFIT3	DOWN	0.62444	0.87810	0.62105	0.79474	0.85391	0.93565	2.09941	2.60848
4	6940086	GYPE	DOWN	7550066	MERTK	UP	0.76635	0.51683	0.69474	0.74211	0.63478	0.57391	2.09587	1.83284
518	1050168	PI3	UP	2810767	EBI3	UP	0.64508	0.84921	0.81579	0.97368	0.63478	0.86783	2.09565	2.69072

443	1440615	OTOF	DOWN	5090215	IFI6	DOWN	0.74540	0.90000	0.63684	0.68947	0.71304	0.92696	2.09528	2.51643
634	520408	IFIT3	DOWN	6940086	GYPE	DOWN	0.67111	0.89841	0.63158	0.68947	0.79130	0.78609	2.09399	2.37397
37	4480730	HBM	DOWN	7550066	MERTK	UP	0.84222	0.51143	0.67895	0.88947	0.57043	0.58609	2.09160	1.98699
520	1050168	PI3	UP	2510356	EMR1	UP	0.64413	0.82095	0.84737	0.95789	0.60000	0.86957	2.09150	2.64841
555	1030100	HS.386275	DOWN	2030309	SERPING1	DOWN	0.73651	0.87206	0.73684	0.61053	0.61739	0.87130	2.09074	2.35389
143	3780452	IFIT1L	DOWN	5550452	KCNMA1	UP	0.74381	0.47333	0.71053	0.66842	0.63478	0.50609	2.08912	1.64784
421	1450358	HBD	DOWN	3850647	PTPN20	UP	0.80381	0.56730	0.74211	0.86316	0.54261	0.54957	2.08852	1.98002
137	3780452	IFIT1L	DOWN	7550066	MERTK	UP	0.75683	0.52413	0.67895	0.70000	0.65217	0.46957	2.08795	1.69369
252	2600747	IFIT2	DOWN	3360343	RSAD2	DOWN	0.75397	0.89683	0.80000	0.82632	0.53391	0.94957	2.08788	2.67271
418	1450358	HBD	DOWN	4040242	FAM89A	UP	0.78444	0.54444	0.66842	0.93158	0.63478	0.65913	2.08765	2.13515
298	2140707	SLPI	UP	2810767	EBI3	UP	0.59111	0.88381	0.80526	1.00000	0.69043	0.92000	2.08681	2.80381
423	1450358	HBD	DOWN	3830735	UPB1	UP	0.76730	0.57206	0.71053	0.95263	0.60696	0.54087	2.08478	2.06556
250	2600747	IFIT2	DOWN	3780187	GYPB	DOWN	0.65048	0.90159	0.60526	0.67368	0.82783	0.87826	2.08357	2.45353
633	520408	IFIT3	DOWN	6980192	HBZ	DOWN	0.62317	0.88254	0.69474	0.61579	0.76522	0.89739	2.08313	2.39572
488	1090390	OAS1	DOWN	2600747	IFIT2	DOWN	0.57810	0.89778	0.70000	0.76842	0.80174	0.95826	2.07983	2.62446
348	2030309	SERPING1	DOWN	2600747	IFIT2	DOWN	0.49587	0.86762	0.67368	0.72632	0.90957	0.92000	2.07912	2.51393
235	2600747	IFIT2	DOWN	6940086	GYPE	DOWN	0.65302	0.90222	0.60000	0.65789	0.82261	0.83652	2.07562	2.39664
351	2030309	SERPING1	DOWN	2120079	EIF2AK2	DOWN	0.74540	0.85365	0.70000	0.63684	0.62783	0.88348	2.07322	2.37397
19	5550452	KCNMA1	UP	6940086	GYPE	DOWN	0.75048	0.51905	0.71053	0.66316	0.61217	0.54261	2.07318	1.72481
446	1440615	OTOF	DOWN	4150600	EIF1AY	DOWN	0.67270	0.87333	0.62105	0.45789	0.77739	0.79652	2.07114	2.12775
244	2600747	IFIT2	DOWN	3990170	IFIT2	DOWN	0.73397	0.93587	0.74737	0.92105	0.58957	0.97739	2.07090	2.83432
43	4480730	HBM	DOWN	5550452	KCNMA1	UP	0.82952	0.54190	0.69474	0.94737	0.54435	0.45739	2.06861	1.94666
9	6510170	IFIT3	DOWN	6980192	HBZ	DOWN	0.63302	0.88571	0.70526	0.64211	0.72870	0.84870	2.06697	2.37652
422	1450358	HBD	DOWN	3830762	TMEM119	UP	0.72476	0.55714	0.77895	0.96316	0.56174	0.49913	2.06545	2.01943
430	1450358	HBD	DOWN	2510356	EMR1	UP	0.78127	0.59270	0.64737	0.89474	0.63478	0.62261	2.06342	2.11004
508	1050168	PI3	UP	4040242	FAM89A	UP	0.64698	0.84952	0.80526	0.96316	0.60696	0.89391	2.05920	2.70659
485	1090390	OAS1	DOWN	3360615	FCER1A	DOWN	0.70476	0.89175	0.55789	0.70000	0.79304	0.92522	2.05570	2.51696
648	520408	IFIT3	DOWN	3780452	IFIT1L	DOWN	0.64032	0.87968	0.63684	0.67895	0.77739	0.80000	2.05455	2.35863
428	1450358	HBD	DOWN	2810767	EBI3	UP	0.78032	0.50921	0.63684	0.95263	0.63652	0.57565	2.05368	2.03749
52	4150600	EIF1AY	DOWN	5550452	KCNMA1	UP	0.75683	0.51016	0.69474	0.71579	0.60174	0.46087	2.05330	1.68682
335	2030309	SERPING1	DOWN	4480730	HBM	DOWN	0.68889	0.89333	0.67368	0.54737	0.69043	0.70783	2.05301	2.14853
10	6510170	IFIT3	DOWN	6940086	GYPE	DOWN	0.68190	0.90571	0.63158	0.71053	0.73913	0.73739	2.05261	2.35363
158	3780187	GYPB	DOWN	6510170	IFIT3	DOWN	0.67937	0.90603	0.62105	0.72105	0.74609	0.78087	2.04650	2.40795
476	1090390	OAS1	DOWN	4150600	EIF1AY	DOWN	0.62635	0.85619	0.64211	0.45263	0.77565	0.77565	2.04411	2.08447
433	1450358	HBD	DOWN	2030309	SERPING1	DOWN	0.69968	0.88476	0.70526	0.47368	0.63826	0.70087	2.04321	2.05932
249	2600747	IFIT2	DOWN	3780452	IFIT1L	DOWN	0.62635	0.89048	0.60526	0.66316	0.80870	0.86087	2.04031	2.41450

141	3780452	IFIT1L	DOWN	6510170	IFIT3	DOWN	0.64825	0.89810	0.66842	0.70526	0.71652	0.75826	2.03320	2.36162
107	3830762	TMEM119	UP	7400747	FAM89A	UP	0.54381	0.82984	0.67368	0.98421	0.81565	0.85217	2.03315	2.66623
51	4150600	EIF1AY	DOWN	5700725	EPSTI1	DOWN	0.62603	0.86286	0.66842	0.39474	0.73739	0.77739	2.03184	2.03499
618	620544	HLA-DRB6	DOWN	2600747	IFIT2	DOWN	0.60159	0.88317	0.67368	0.68421	0.75304	0.92870	2.02831	2.49608
57	4040242	FAM89A	UP	7400747	FAM89A	UP	0.56508	0.82444	0.59474	0.96842	0.86435	0.86261	2.02416	2.65547
46	4150600	EIF1AY	DOWN	7550066	MERTK	UP	0.75460	0.50730	0.65263	0.74211	0.61565	0.57043	2.02289	1.81984
204	3360343	RSAD2	DOWN	3870338	IFI44L	DOWN	0.68254	0.89683	0.65789	0.84211	0.68174	0.96870	2.02217	2.70763
269	2510356	EMR1	UP	3830762	TMEM119	UP	0.57524	0.82000	0.71053	0.97895	0.73565	0.74783	2.02142	2.54677
234	2600747	IFIT2	DOWN	6980192	HBZ	DOWN	0.60349	0.87651	0.65789	0.61579	0.76000	0.88696	2.02139	2.37925
484	1090390	OAS1	DOWN	3780187	GYPB	DOWN	0.64095	0.90254	0.58421	0.62105	0.79304	0.81043	2.01821	2.33403
635	520408	IFIT3	DOWN	6510170	IFIT3	DOWN	0.59968	0.88190	0.56316	0.81053	0.85043	0.94261	2.01328	2.63504
588	1010546	LOC649143	DOWN	2030309	SERPING1	DOWN	0.69873	0.87302	0.64737	0.56316	0.66609	0.71652	2.01219	2.15270
469	1090390	OAS1	DOWN	6940086	GYPE	DOWN	0.64000	0.90349	0.57895	0.62632	0.79304	0.76348	2.01199	2.29329
102	3850647	PTPN20	UP	4150600	EIF1AY	DOWN	0.77238	0.52857	0.72632	0.78947	0.51130	0.52348	2.01000	1.84152
454	1440615	OTOF	DOWN	3780187	GYPB	DOWN	0.65810	0.90540	0.56316	0.62105	0.78609	0.84696	2.00734	2.37341
439	1440615	OTOF	DOWN	6940086	GYPE	DOWN	0.65810	0.90857	0.57895	0.61579	0.76870	0.77043	2.00574	2.29480
36	4670327	FBXO7	DOWN	5090215	IFI6	DOWN	0.67619	0.88984	0.61579	0.51579	0.71304	0.76000	2.00502	2.16563
308	2120079	EIF2AK2	DOWN	5090215	IFI6	DOWN	0.64254	0.87365	0.73158	0.65263	0.62609	0.88174	2.00021	2.40802
309	2120079	EIF2AK2	DOWN	4670327	FBXO7	DOWN	0.62825	0.86508	0.56316	0.59474	0.80522	0.89739	1.99663	2.35721
292	2140707	SLPI	UP	3830762	TMEM119	UP	0.61619	0.81206	0.60526	0.98947	0.77391	0.84696	1.99537	2.64849
330	2030309	SERPING1	DOWN	6510170	IFIT3	DOWN	0.64381	0.86857	0.66842	0.78421	0.67826	0.87304	1.99049	2.52583
536	1030100	HS.386275	DOWN	5090215	IFI6	DOWN	0.61048	0.89968	0.79474	0.59474	0.57913	0.89739	1.98434	2.39181
44	4480730	HBM	DOWN	5090215	IFI6	DOWN	0.62095	0.89905	0.65789	0.54737	0.70261	0.69217	1.98146	2.13859
569	1010546	LOC649143	DOWN	5090215	IFI6	DOWN	0.63968	0.88603	0.67368	0.53684	0.66783	0.76348	1.98119	2.18635
56	4040242	FAM89A	UP	7550066	MERTK	UP	0.55302	0.83238	0.63158	0.97368	0.79652	0.77043	1.98112	2.57650
414	1450358	HBD	DOWN	5090215	IFI6	DOWN	0.64381	0.86063	0.70000	0.55789	0.63652	0.65913	1.98033	2.07766
237	2600747	IFIT2	DOWN	5700725	EPSTI1	DOWN	0.56254	0.89492	0.57895	0.76316	0.83826	0.94087	1.97975	2.59895
498	1050168	PI3	UP	7400747	FAM89A	UP	0.63778	0.85460	0.80526	0.95789	0.53043	0.91478	1.97348	2.72728
413	1450358	HBD	DOWN	5550452	KCNMA1	UP	0.74254	0.53778	0.64737	0.91053	0.57739	0.47652	1.96730	1.92483
483	1090390	OAS1	DOWN	3780452	IFIT1L	DOWN	0.61778	0.88095	0.58947	0.62632	0.76000	0.78435	1.96725	2.29162
453	1440615	OTOF	DOWN	3780452	IFIT1L	DOWN	0.64032	0.89270	0.57368	0.56316	0.75304	0.78957	1.96705	2.24542
666	520408	IFIT3	DOWN	620544	HLA-DRB6	DOWN	0.60921	0.88762	0.65789	0.73158	0.69913	0.88696	1.96623	2.50615
203	3360343	RSAD2	DOWN	3990170	IFI27	DOWN	0.66413	0.92952	0.71053	0.92632	0.58957	0.97217	1.96422	2.82801
626	620544	HLA-DRB6	DOWN	1440615	OTOF	DOWN	0.63937	0.88381	0.64211	0.67368	0.68174	0.88348	1.96321	2.44097
455	1440615	OTOF	DOWN	3360615	FCER1A	DOWN	0.71556	0.89238	0.43684	0.73158	0.80870	0.92000	1.96109	2.54396
103	3850647	PTPN20	UP	4040242	FAM89A	UP	0.57524	0.84921	0.53158	0.97368	0.85391	0.79652	1.96073	2.61941

407	1450358	HBD	DOWN	7550066	MERTK	UP		0.76603	0.56317	0.60000	0.91053	0.59304	0.44696	1.95908	1.92066
62	4040242	FAM89A	UP	5550452	KCNMA1	UP		0.58794	0.84095	0.63684	0.99474	0.73043	0.84522	1.95521	2.68091
278	2140707	SLPI	UP	7400747	FAM89A	UP		0.56159	0.87143	0.82105	0.99474	0.57217	0.93043	1.95481	2.79660
468	1090390	OAS1	DOWN	6980192	HBZ	DOWN		0.58190	0.87333	0.62105	0.57368	0.75130	0.86435	1.95426	2.31137
93	3850647	PTPN20	UP	7400747	FAM89A	UP		0.56349	0.84317	0.50526	0.96842	0.88522	0.87130	1.95397	2.68290
675	150315	C21ORF7	DOWN	4670327	FBX07	DOWN		0.57937	0.77841	0.63684	0.47895	0.73739	0.75826	1.95360	2.01562
225	2810767	EBI3	UP	3850647	PTPN20	UP		0.55333	0.84063	0.53684	0.97895	0.85739	0.79652	1.94757	2.61610
320	2120079	EIF2AK2	DOWN	3360615	FCER1A	DOWN		0.54984	0.86317	0.65789	0.57368	0.73913	0.90957	1.94687	2.34642
142	3780452	IFIT1L	DOWN	5700725	EPSTI1	DOWN		0.62222	0.88603	0.58421	0.65263	0.73043	0.76870	1.93687	2.30736
438	1440615	OTOF	DOWN	6980192	HBZ	DOWN		0.62254	0.88794	0.61579	0.59474	0.69739	0.89739	1.93572	2.38006
300	2140707	SLPI	UP	2510356	EMR1	UP		0.55238	0.83778	0.81579	1.00000	0.56000	0.90783	1.92817	2.74560
600	620544	HLA-DRB6	DOWN	6510170	IFIT3	DOWN		0.63333	0.88540	0.66316	0.72632	0.62957	0.84696	1.92606	2.45867
365	2000148	IFIT1	DOWN	3870338	IF44L	DOWN		0.61016	0.90349	0.71053	0.82105	0.60174	0.96348	1.92242	2.68802
310	2120079	EIF2AK2	DOWN	4480730	HBM	DOWN		0.55492	0.88984	0.61579	0.62105	0.74783	0.78435	1.91854	2.29524
117	3830762	TMEM119	UP	4040242	FAM89A	UP		0.52571	0.83397	0.67368	0.98421	0.71652	0.79826	1.91592	2.61644
15	5700725	EPSTI1	DOWN	6510170	IFIT3	DOWN		0.65429	0.89048	0.69474	0.81579	0.56348	0.92870	1.91250	2.63496
601	620544	HLA-DRB6	DOWN	5700725	EPSTI1	DOWN		0.58571	0.88190	0.65263	0.67895	0.67130	0.87130	1.90965	2.43216
521	1050168	PI3	UP	2140707	SLPI	UP		0.65333	0.79492	0.66316	0.96842	0.59304	0.85217	1.90953	2.61552
98	3850647	PTPN20	UP	5550452	KCNMA1	UP		0.57365	0.84000	0.61579	0.98947	0.71652	0.59826	1.90596	2.42773
554	1030100	HS.386275	DOWN	2120079	EIF2AK2	DOWN		0.54762	0.87683	0.57368	0.51053	0.78261	0.94435	1.90391	2.33170
344	2030309	SERPING1	DOWN	3780187	GYPB	DOWN		0.63937	0.89206	0.56842	0.61053	0.69565	0.72000	1.90344	2.22259
92	3850647	PTPN20	UP	7550066	MERTK	UP		0.57048	0.83746	0.61053	0.98421	0.72000	0.71130	1.90100	2.53298
410	1450358	HBD	DOWN	6940086	GYPE	DOWN		0.57968	0.67873	0.72632	0.55789	0.58957	0.56174	1.89556	1.79836
432	1450358	HBD	DOWN	2120079	EIF2AK2	DOWN		0.58540	0.84476	0.62632	0.63684	0.68348	0.73391	1.89519	2.21552
548	1030100	HS.386275	DOWN	3360615	FCER1A	DOWN		0.56667	0.87333	0.66842	0.58421	0.65913	0.86609	1.89422	2.32363
537	1030100	HS.386275	DOWN	4670327	FBX07	DOWN		0.63873	0.90889	0.52632	0.62632	0.72870	0.82435	1.89374	2.35955
329	2030309	SERPING1	DOWN	6940086	GYPE	DOWN		0.63651	0.89048	0.57368	0.61053	0.68348	0.68522	1.89367	2.18622
403	1510424	S100P	UP	2140707	SLPI	UP		0.64222	0.87492	0.55263	0.99474	0.69739	0.91478	1.89225	2.78444
492	1090390	OAS1	DOWN	2030309	SERPING1	DOWN		0.55079	0.87937	0.53684	0.71579	0.80348	0.88870	1.89111	2.48385
336	2030309	SERPING1	DOWN	4150600	EIF1AY	DOWN		0.62508	0.85079	0.61053	0.43684	0.65391	0.68174	1.88952	1.96937
653	520408	IFIT3	DOWN	2600747	IFIT2	DOWN		0.58635	0.87556	0.58947	0.79474	0.70957	0.96000	1.88539	2.63029
13	5700725	EPSTI1	DOWN	6980192	HBZ	DOWN		0.58603	0.87619	0.58421	0.59474	0.70957	0.85565	1.87981	2.32658
458	1440615	OTOF	DOWN	2600747	IFIT2	DOWN		0.56825	0.89810	0.59474	0.71579	0.71304	0.95478	1.87603	2.56867
372	2000148	IFIT1	DOWN	3360343	RSAD2	DOWN		0.60762	0.89524	0.52105	0.81053	0.74435	0.96000	1.87302	2.66576
180	3360615	FCER1A	DOWN	4670327	FBX07	DOWN		0.55587	0.76159	0.64737	0.46316	0.66957	0.68348	1.87281	1.90822
288	2140707	SLPI	UP	4040242	FAM89A	UP		0.57492	0.86571	0.82105	0.99474	0.47130	0.91826	1.86728	2.77871

159	3780187	GYPB	DOWN	5700725	EPSTI1	DOWN	0.64444	0.89810	0.42632	0.66842	0.79478	0.79652	1.86554	2.36304
136	3830735	UPB1	UP	3830762	TMEM119	UP	0.55429	0.79937	0.67895	0.98947	0.62957	0.73391	1.86280	2.52275
627	620544	HLA-DRB6	DOWN	1090390	OAS1	DOWN	0.58508	0.88317	0.60526	0.65789	0.66609	0.87478	1.85643	2.41585
255	2510356	EMR1	UP	7400747	FAM89A	UP	0.55746	0.83333	0.57895	0.98947	0.71826	0.87130	1.85467	2.69411
425	1450358	HBD	DOWN	3780187	GYPB	DOWN	0.56984	0.67873	0.71579	0.55263	0.56696	0.56870	1.85259	1.80006
440	1440615	OTOF	DOWN	6510170	IFIT3	DOWN	0.51683	0.90540	0.67368	0.75789	0.66087	0.94783	1.85138	2.61112
424	1450358	HBD	DOWN	3780452	IFIT1L	DOWN	0.59683	0.67270	0.71579	0.45263	0.53739	0.56870	1.85001	1.69403
14	5700725	EPSTI1	DOWN	6940086	GYPE	DOWN	0.64508	0.89968	0.43158	0.66842	0.77217	0.76174	1.84883	2.32984
636	520408	IFIT3	DOWN	5700725	EPSTI1	DOWN	0.61397	0.89778	0.60000	0.81053	0.63130	0.94087	1.84527	2.64917
254	2510356	EMR1	UP	7550066	MERTK	UP	0.60000	0.81683	0.55789	0.97368	0.68348	0.77565	1.84137	2.56616
686	150315	C21ORF7	DOWN	3360615	FCER1A	DOWN	0.55714	0.82603	0.56316	0.63158	0.71826	0.81913	1.83856	2.27674
693	150315	C21ORF7	DOWN	2030309	SERPING1	DOWN	0.68889	0.88889	0.58421	0.71579	0.56348	0.89739	1.83658	2.50207
270	2510356	EMR1	UP	3830735	UPB1	UP	0.54635	0.82159	0.54737	0.99474	0.73739	0.79130	1.83111	2.60763
268	2510356	EMR1	UP	3850647	PTPN20	UP	0.47619	0.83143	0.53684	0.97368	0.81565	0.79304	1.82868	2.59816
343	2030309	SERPING1	DOWN	3780452	IFIT1L	DOWN	0.61397	0.88667	0.57368	0.60526	0.63652	0.69913	1.82417	2.19106
179	3360615	FCER1A	DOWN	5090215	IFIG	DOWN	0.61810	0.87460	0.55263	0.64211	0.65217	0.81043	1.82290	2.32714
122	3830735	UPB1	UP	7400747	FAM89A	UP	0.50381	0.84603	0.48947	1.00000	0.82957	0.87826	1.82285	2.72429
692	150315	C21ORF7	DOWN	2120079	EIF2AK2	DOWN	0.55524	0.90286	0.56316	0.59474	0.70261	0.93565	1.82100	2.43325
112	3830762	TMEM119	UP	5550452	KCNMA1	UP	0.53651	0.78159	0.70000	0.99474	0.58435	0.68174	1.82086	2.45806
587	1010546	LOC649143	DOWN	2120079	EIF2AK2	DOWN	0.58349	0.85397	0.52105	0.58947	0.70957	0.83478	1.81411	2.27822
701	150315	C21ORF7	DOWN	1010546	LOC649143	DOWN	0.55429	0.81492	0.63158	0.50000	0.62261	0.69565	1.80847	2.01057
135	3830735	UPB1	UP	3850647	PTPN20	UP	0.49302	0.83238	0.52105	0.98421	0.78435	0.74435	1.79842	2.56094
226	2810767	EBI3	UP	3830762	TMEM119	UP	0.50730	0.81111	0.68947	0.99474	0.60000	0.82435	1.79678	2.63020
333	2030309	SERPING1	DOWN	5090215	IFIG	DOWN	0.68667	0.86127	0.60526	0.71053	0.50087	0.82957	1.79280	2.40136
106	3830762	TMEM119	UP	7550066	MERTK	UP	0.53206	0.81714	0.70526	0.98421	0.55478	0.70783	1.79211	2.50918
345	2030309	SERPING1	DOWN	3360615	FCER1A	DOWN	0.69079	0.86889	0.44211	0.68421	0.65913	0.83826	1.79203	2.39136
676	150315	C21ORF7	DOWN	4480730	HBM	DOWN	0.48317	0.83206	0.66842	0.54211	0.64000	0.67826	1.79160	2.05243
331	2030309	SERPING1	DOWN	5700725	EPSTI1	DOWN	0.52317	0.87111	0.56842	0.71579	0.69913	0.88870	1.79073	2.47560
328	2030309	SERPING1	DOWN	6980192	HBZ	DOWN	0.57968	0.86476	0.58947	0.45263	0.62087	0.77565	1.79003	2.09305
120	3830762	TMEM119	UP	3850647	PTPN20	UP	0.55841	0.82127	0.55789	0.97368	0.67304	0.59826	1.78935	2.39321
181	3360615	FCER1A	DOWN	4480730	HBM	DOWN	0.52889	0.80413	0.66316	0.53158	0.59478	0.59478	1.78683	1.93049
145	3780452	IFIT1L	DOWN	4670327	FBXO7	DOWN	0.61333	0.67492	0.57895	0.49474	0.59304	0.57913	1.78532	1.74879
132	3830735	UPB1	UP	4040242	FAM89A	UP	0.51333	0.84317	0.53684	1.00000	0.73217	0.83652	1.78235	2.67970
604	620544	HLA-DRB6	DOWN	4670327	FBXO7	DOWN	0.61111	0.79365	0.57368	0.57368	0.59304	0.65565	1.77784	2.02299
319	2120079	EIF2AK2	DOWN	3780187	GYPB	DOWN	0.53429	0.84095	0.48421	0.52632	0.75304	0.76696	1.77154	2.13422
625	620544	HLA-DRB6	DOWN	1450358	HBD	DOWN	0.57460	0.78000	0.60526	0.63158	0.58957	0.62957	1.76943	2.04114

311	2120079	EIF2AK2	DOWN	4150600	EIF1AY	DOWN	0.48444	0.80254	0.56842	0.56316	0.71652	0.76000	1.76939	2.12570
260	2510356	EMR1	UP	5550452	KCNMA1	UP	0.58254	0.80889	0.43684	1.00000	0.74957	0.78957	1.76895	2.59845
558	1030100	HS.386275	DOWN	1450358	HBD	DOWN	0.59016	0.87397	0.60526	0.66842	0.56696	0.66957	1.76238	2.21195
217	2810767	EBI3	UP	5550452	KCNMA1	UP	0.54730	0.83905	0.54737	1.00000	0.66522	0.80522	1.75989	2.64427
31	4670327	FBXO7	DOWN	6980192	HBZ	DOWN	0.61556	0.71365	0.57368	0.56842	0.56870	0.60348	1.75794	1.88555
304	2120079	EIF2AK2	DOWN	6940086	GYPE	DOWN	0.53048	0.84286	0.48421	0.50526	0.73739	0.72174	1.75208	2.06986
275	2510356	EMR1	UP	2810767	EBI3	UP	0.60444	0.85079	0.52105	1.00000	0.62087	0.85739	1.74637	2.70818
661	520408	IFIT3	DOWN	1440615	OTOF	DOWN	0.52159	0.90413	0.67368	0.75789	0.54783	0.96000	1.74310	2.62202
547	1030100	HS.386275	DOWN	3780187	GYPB	DOWN	0.53587	0.86762	0.51579	0.53158	0.69043	0.73043	1.74210	2.12963
415	1450358	HBD	DOWN	4670327	FBXO7	DOWN	0.56413	0.66984	0.64211	0.58947	0.53565	0.56000	1.74188	1.81931
144	3780452	IFIT1L	DOWN	5090215	IFI6	DOWN	0.54698	0.83333	0.53158	0.57368	0.66087	0.66783	1.73943	2.07484
364	2000148	IFIT1	DOWN	3990170	IFI27	DOWN	0.62063	0.93333	0.60000	0.92632	0.51826	0.97565	1.73890	2.83530
622	620544	HLA-DRB6	DOWN	2030309	SERPING1	DOWN	0.59270	0.86413	0.57368	0.68421	0.57043	0.77565	1.73682	2.32399
32	4670327	FBXO7	DOWN	6940086	GYPE	DOWN	0.61270	0.68476	0.59474	0.49474	0.52870	0.54783	1.73613	1.72732
700	150315	C21ORF7	DOWN	1030100	HS.386275	DOWN	0.59143	0.93079	0.60526	0.59474	0.53739	0.92522	1.73408	2.45075
91	3870338	IFI44L	DOWN	3990170	IFI27	DOWN	0.60794	0.93016	0.60000	0.93684	0.52174	0.97043	1.72968	2.83744
409	1450358	HBD	DOWN	6980192	HBZ	DOWN	0.58381	0.71397	0.58947	0.56316	0.55478	0.60696	1.72807	1.88408
162	3780187	GYPB	DOWN	4670327	FBXO7	DOWN	0.60698	0.68349	0.57368	0.48947	0.54609	0.56348	1.72676	1.73644
121	3830735	UPB1	UP	7550066	MERTK	UP	0.54508	0.82825	0.65263	1.00000	0.52870	0.73043	1.72641	2.55869
25	5090215	IFI6	DOWN	6940086	GYPE	DOWN	0.56286	0.85365	0.46316	0.56842	0.69913	0.66261	1.72515	2.08468
212	2810767	EBI3	UP	7400747	FAM89A	UP	0.53937	0.87365	0.47895	1.00000	0.70609	0.89913	1.72440	2.77278
161	3780187	GYPB	DOWN	5090215	IFI6	DOWN	0.56857	0.85270	0.45263	0.56842	0.70087	0.69565	1.72207	2.11677
615	620544	HLA-DRB6	DOWN	3360615	FCER1A	DOWN	0.59206	0.77873	0.57895	0.59474	0.54957	0.71478	1.72058	2.08825
595	1010546	LOC649143	DOWN	1030100	HS.386275	DOWN	0.60762	0.86413	0.49474	0.56316	0.61739	0.72174	1.71975	2.14902
416	1450358	HBD	DOWN	4480730	HBM	DOWN	0.59365	0.71778	0.62105	0.63684	0.50435	0.54261	1.71905	1.89723
674	150315	C21ORF7	DOWN	5090215	IFI6	DOWN	0.62254	0.92254	0.49474	0.72105	0.59826	0.88348	1.71554	2.52707
318	2120079	EIF2AK2	DOWN	3780452	IFIT1L	DOWN	0.51619	0.82476	0.49474	0.51579	0.70087	0.73565	1.71180	2.07620
605	620544	HLA-DRB6	DOWN	4480730	HBM	DOWN	0.53937	0.81587	0.58421	0.57895	0.58783	0.61217	1.71140	2.00699
156	3780187	GYPB	DOWN	6980192	HBZ	DOWN	0.53937	0.71238	0.56316	0.51053	0.60522	0.59826	1.70774	1.82117
496	1090390	OAS1	DOWN	1440615	OTOF	DOWN	0.60794	0.89746	0.52105	0.67368	0.56870	0.95130	1.69768	2.52245
39	4480730	HBM	DOWN	6980192	HBZ	DOWN	0.53333	0.74476	0.61053	0.55263	0.55304	0.58087	1.69690	1.87826
53	4150600	EIF1AY	DOWN	5090215	IFI6	DOWN	0.45841	0.81619	0.61579	0.52105	0.61913	0.69043	1.69333	2.02768
630	620544	HLA-DRB6	DOWN	1010546	LOC649143	DOWN	0.59143	0.78603	0.51579	0.57895	0.58609	0.63130	1.69331	1.99628
45	4480730	HBM	DOWN	4670327	FBXO7	DOWN	0.64286	0.72286	0.57895	0.60000	0.46783	0.53565	1.68963	1.85851
303	2120079	EIF2AK2	DOWN	6980192	HBZ	DOWN	0.51619	0.82000	0.47368	0.47368	0.69913	0.85217	1.68901	2.14586
6	6940086	GYPE	DOWN	6980192	HBZ	DOWN	0.53619	0.71175	0.56842	0.52632	0.58087	0.61043	1.68548	1.84850

532	1030100	HS.386275	DOWN	6940086	GYPE	DOWN	0.53556	0.86857	0.51579	0.51053	0.63130	0.69391	1.68265	2.07301
581	1010546	LOC649143	DOWN	3360615	FCER1A	DOWN	0.50381	0.74825	0.67368	0.51053	0.50435	0.66609	1.68184	1.92487
462	1440615	OTOF	DOWN	2030309	SERPING1	DOWN	0.44508	0.88381	0.50526	0.67368	0.72870	0.90609	1.67904	2.46358
265	2510356	EMR1	UP	4040242	FAM89A	UP	0.57778	0.82889	0.54737	0.98947	0.54783	0.82609	1.67297	2.64445
685	150315	C21ORF7	DOWN	3780187	GYPB	DOWN	0.50222	0.78000	0.50526	0.53684	0.66261	0.67826	1.67009	1.99510
621	620544	HLA-DRB6	DOWN	2120079	EIF2AK2	DOWN	0.54095	0.83778	0.51053	0.47895	0.61565	0.85913	1.66713	2.17586
669	150315	C21ORF7	DOWN	6980192	HBZ	DOWN	0.54571	0.78540	0.53158	0.47895	0.58957	0.75652	1.66686	2.02087
24	5090215	IF16	DOWN	6980192	HBZ	DOWN	0.49143	0.83905	0.55789	0.53158	0.61217	0.77391	1.66150	2.14454
426	1450358	HBD	DOWN	3360615	FCER1A	DOWN	0.53016	0.75746	0.68421	0.54211	0.44348	0.58957	1.65785	1.88913
565	1010546	LOC649143	DOWN	6940086	GYPE	DOWN	0.53651	0.76159	0.55263	0.47368	0.56870	0.58087	1.65784	1.81614
580	1010546	LOC649143	DOWN	3780187	GYPB	DOWN	0.53365	0.76032	0.55263	0.47895	0.56522	0.59304	1.65150	1.83231
546	1030100	HS.386275	DOWN	3780452	IFIT1L	DOWN	0.51619	0.84698	0.54211	0.52632	0.58783	0.69913	1.64612	2.07243
190	3360615	FCER1A	DOWN	3780187	GYPB	DOWN	0.52190	0.76317	0.46842	0.43684	0.65217	0.65391	1.64250	1.85393
570	1010546	LOC649143	DOWN	4670327	FBXO7	DOWN	0.54825	0.75619	0.52632	0.60526	0.56696	0.59304	1.64153	1.95450
222	2810767	EBI3	UP	4040242	FAM89A	UP	0.53238	0.87746	0.51579	1.00000	0.59130	0.86783	1.63947	2.74529
599	620544	HLA-DRB6	DOWN	6940086	GYPE	DOWN	0.53683	0.79111	0.50000	0.50000	0.60000	0.61739	1.63683	1.90850
48	4150600	EIF1AY	DOWN	6980192	HBZ	DOWN	0.53937	0.73111	0.51579	0.55789	0.58087	0.59304	1.63602	1.88205
163	3780187	GYPB	DOWN	4480730	HBM	DOWN	0.51365	0.71937	0.63158	0.45263	0.49043	0.56174	1.63566	1.73374
157	3780187	GYPB	DOWN	6940086	GYPE	DOWN	0.52222	0.67968	0.56842	0.51053	0.54435	0.56348	1.63499	1.75369
139	3780452	IFIT1L	DOWN	6980192	HBZ	DOWN	0.52762	0.70825	0.53158	0.53158	0.57565	0.61043	1.63485	1.85027
670	150315	C21ORF7	DOWN	6940086	GYPE	DOWN	0.50667	0.77492	0.51053	0.52105	0.61739	0.64522	1.63458	1.94119
531	1030100	HS.386275	DOWN	6980192	HBZ	DOWN	0.50984	0.83937	0.49474	0.51579	0.62783	0.80000	1.63240	2.15515
171	3780187	GYPB	DOWN	3780452	IFIT1L	DOWN	0.53746	0.67714	0.46842	0.51053	0.62435	0.59130	1.63023	1.77897
614	620544	HLA-DRB6	DOWN	3780187	GYPB	DOWN	0.53714	0.79333	0.49474	0.50000	0.59652	0.62261	1.62840	1.91594
538	1030100	HS.386275	DOWN	4480730	HBM	DOWN	0.56095	0.91587	0.43684	0.63684	0.62783	0.68696	1.62562	2.23967
603	620544	HLA-DRB6	DOWN	5090215	IF16	DOWN	0.50984	0.86000	0.57368	0.60526	0.54087	0.75826	1.62440	2.22352
441	1440615	OTOF	DOWN	5700725	EPST1L	DOWN	0.58762	0.90095	0.48947	0.72632	0.54609	0.94435	1.62318	2.57162
684	150315	C21ORF7	DOWN	3780452	IFIT1L	DOWN	0.51619	0.75937	0.53158	0.52632	0.57391	0.67478	1.62168	1.96046
40	4480730	HBM	DOWN	6940086	GYPE	DOWN	0.49556	0.72159	0.60526	0.46316	0.52000	0.54435	1.62082	1.72909
525	1050168	PI3	UP	1510424	S100P	UP	0.52762	0.87238	0.65263	1.00000	0.44000	0.92000	1.62025	2.79238
417	1450358	HBD	DOWN	4150600	EIF1AY	DOWN	0.52286	0.70254	0.55263	0.62632	0.54435	0.44348	1.61984	1.77233
127	3830735	UPB1	UP	5550452	KCNMA1	UP	0.56190	0.81365	0.45263	1.00000	0.60000	0.78087	1.61454	2.59452
140	3780452	IFIT1L	DOWN	6940086	GYPE	DOWN	0.53143	0.67841	0.50000	0.52105	0.57913	0.58261	1.61056	1.78207
471	1090390	OAS1	DOWN	5700725	EPST1L	DOWN	0.50571	0.90381	0.63158	0.78947	0.47304	0.94087	1.61034	2.63415
564	1010546	LOC649143	DOWN	6980192	HBZ	DOWN	0.57683	0.74413	0.52632	0.43158	0.50435	0.64696	1.60749	1.82266
146	3780452	IFIT1L	DOWN	4480730	HBM	DOWN	0.49302	0.71619	0.58421	0.53684	0.52696	0.56174	1.60418	1.81477

591	1010546	LOC649143	DOWN	1450358	HBD	DOWN	0.51905	0.74159	0.54737	0.64737	0.53565	0.58087	1.60207	1.96983
702	150315	C21ORF7	DOWN	620544	HLA-DRB6	DOWN	0.56762	0.83460	0.50526	0.55789	0.52522	0.76870	1.59810	2.16119
579	1010546	LOC649143	DOWN	3780452	IFIT1L	DOWN	0.53365	0.74635	0.53158	0.50526	0.53043	0.59826	1.59566	1.84987
147	3780452	IFIT1L	DOWN	4150600	EIF1AY	DOWN	0.52095	0.70825	0.53158	0.51579	0.54261	0.57739	1.59514	1.80143
16	5550452	KCNMA1	UP	7550066	MERTK	UP	0.54413	0.82317	0.48421	0.99474	0.55304	0.71826	1.58138	2.53617
696	150315	C21ORF7	DOWN	1450358	HBD	DOWN	0.45460	0.76508	0.71579	0.58421	0.40870	0.65739	1.57909	2.00668
175	3360615	FCER1A	DOWN	6940086	GYPE	DOWN	0.52571	0.76413	0.48421	0.45789	0.56870	0.61565	1.57862	1.83767
211	2810767	EBI3	UP	7550066	MERTK	UP	0.52381	0.84254	0.58421	1.00000	0.46783	0.78087	1.57585	2.62341
55	4150600	EIF1AY	DOWN	4480730	HBM	DOWN	0.48190	0.73937	0.55263	0.65263	0.54087	0.52870	1.57541	1.92069
613	620544	HLA-DRB6	DOWN	3780452	IFIT1L	DOWN	0.52476	0.77968	0.48421	0.51053	0.56348	0.63478	1.57245	1.92499
572	1010546	LOC649143	DOWN	4150600	EIF1AY	DOWN	0.48635	0.72603	0.55263	0.59474	0.53043	0.57565	1.56942	1.89642
182	3360615	FCER1A	DOWN	4150600	EIF1AY	DOWN	0.53619	0.74952	0.58421	0.48421	0.43304	0.63130	1.55344	1.86504
164	3780187	GYPB	DOWN	4150600	EIF1AY	DOWN	0.49905	0.70857	0.53684	0.53684	0.51304	0.43304	1.54893	1.67846
598	620544	HLA-DRB6	DOWN	6980192	HBZ	DOWN	0.50635	0.77905	0.54211	0.50526	0.49913	0.66087	1.54758	1.94518
227	2810767	EBI3	UP	3830735	UPB1	UP	0.56159	0.84762	0.49474	1.00000	0.48522	0.85391	1.54154	2.70153
189	3360615	FCER1A	DOWN	3780452	IFIT1L	DOWN	0.53397	0.75333	0.52632	0.56316	0.47304	0.62957	1.53333	1.94606
54	4150600	EIF1AY	DOWN	4670327	FBXO7	DOWN	0.55238	0.69841	0.48421	0.59474	0.49565	0.58087	1.53224	1.87402
49	4150600	EIF1AY	DOWN	6940086	GYPE	DOWN	0.49746	0.71143	0.53158	0.52632	0.50087	0.44522	1.52991	1.68296
606	620544	HLA-DRB6	DOWN	4150600	EIF1AY	DOWN	0.47111	0.76000	0.46316	0.54737	0.58783	0.63478	1.52210	1.94215
174	3360615	FCER1A	DOWN	6980192	HBZ	DOWN	0.56286	0.75460	0.42632	0.47368	0.53217	0.70957	1.52135	1.93785
571	1010546	LOC649143	DOWN	4480730	HBM	DOWN	0.55937	0.81397	0.47895	0.40526	0.46957	0.45391	1.50788	1.67314
629	620544	HLA-DRB6	DOWN	1030100	HS.386275	DOWN	0.46540	0.85238	0.51579	0.49474	0.50609	0.77739	1.48727	2.12451
677	150315	C21ORF7	DOWN	4150600	EIF1AY	DOWN	0.50000	0.76063	0.56842	0.49474	0.38261	0.68348	1.45103	1.93885
539	1030100	HS.386275	DOWN	4150600	EIF1AY	DOWN	0.47365	0.82095	0.45789	0.61579	0.36696	0.69217	1.29850	2.12892

* Expression level of transcript in subject with definite bacterial infection. Up = gene expression is up-regulated in subject with bacterial infection, Down = gene expression level is down-regulated in subject with bacterial infection.

^ opposite = one gene in signature is up-regulated whilst other gene in signature is down-regulated in subject with bacterial infection.

same = both genes in signature are up-regulated or both genes in signature are down-regulated in subject with bacterial infection.

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CLAIMS

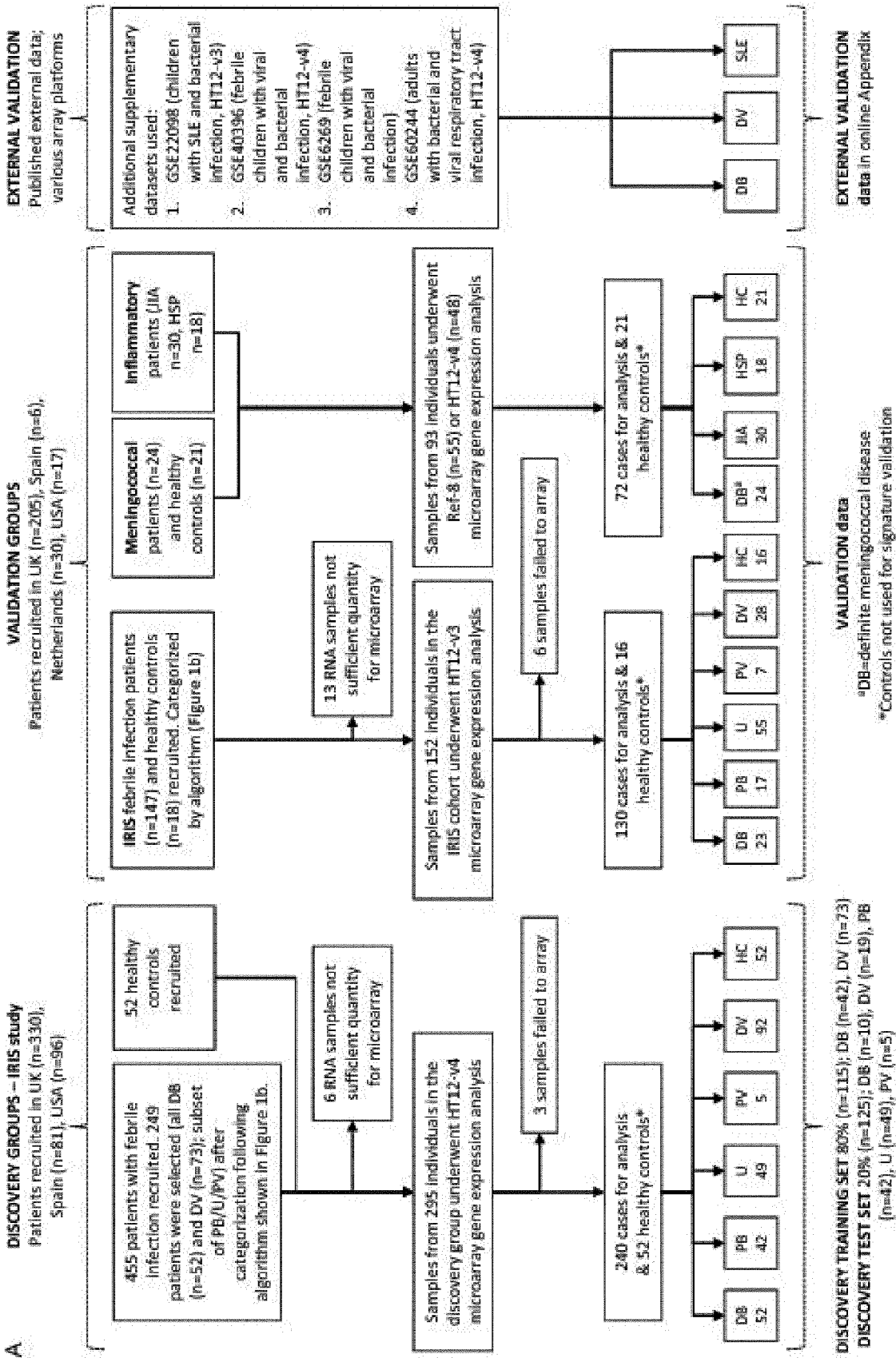
1. A method for identifying a subject having a bacterial infection comprising detecting in a subject derived RNA sample the modulation in gene expression levels of a gene signature comprising two or more genes, but no more than 10 genes, selected from the group consisting of: *IFI44L*, *FAM89A*, *IFI27L*, *IFT11*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD*, *FBXO7*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
2. The method according to claim 1, wherein the gene signature comprises two or more genes but no more than 10 genes selected from the group consisting of: *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *ESPTI1*, *OAS1*, *IFI6*, *HS.386275*, *EIF2AK2*, *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
3. The method according to claims 1 or 2, wherein the gene signature comprises at least one gene selected from the group consisting of:
 - a) *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *OAS1*, *IFI6*, *HS.386275*, *EIF2AK2*; and optionally one or more genes selected from the group consisting of:
 - b) *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
4. A method according to any one of the preceding claims, wherein the gene signature is based on two genes of primary importance.
5. A method according to any one of the preceding claims, wherein the gene signature comprises one or more of the following pairs of genes: *IFI44L* and *FAM89A*, *OAS1* and *EMR1*, *EMR1* and *IFI44L*, *OSA1* and *FAM89A*, *EBI3* and *IFI44L*, *S100P* and *RSAD2*, *SLPI* and *IFI44L*, *S100P* and *EPSTI1*, *S100P* and *IFI44L*, *OAS1* and *FAM89A*, *EMR1* and *RSAD2*, *IFIT3* and *FAM89A*, *TMEM119* and *IFI44L*, *IFIT3* and *EMR1*, *IFI6* and *FAM89A*, *EPSTI1* and *FAM89A*, *IFIT3* and *FAM89A*, *UPB1* and *IFI44L*, *S100P* and *IFIT1*, *RSAD2* and *FAM89A*, *EMR1* and *EPSTI1*, *S100P* and *EIF2AK2*, *IFIT3* and *FAM89A*, *OAS1* and *SLPI*, *IFIT1* and *FAM89A*, *IFIT3* and *SLPI*, *EMR1* and *IFIT3*, *OAS1* and *S100P*, *IFIT1* and *SLPI*, *IFIT1* and *EMR1*, *FAM89A* and *EPSTI1*, *SLPI* and *RSAD2*, *S100P* and *IFIT2*, *IFIT1* and *TMEM119*, *IFIT1* and *FAM89A*, *SLPI* and *EPSTI1*, *FAM89A* and *IFIT3*, *OAS1* and *EBI3*, *EIF2AK2* and *FAM89A*, *EBI3* and *EPSTI1*, *IFIT3* and *S100P*, *S100P* and *IFI6*, *OTOF* and *S100P*, *OAS1* and *TMEM119*, *EBI3* and *RSAD2*, *OTOF* and *EBI3*, *S100P* and *IFIT3*, *OTOF* and *FAM89A*, *IFIT2* and *FAM89A*, *IFI27* and *FAM89A*, *OAS1* and *UPB1*, *OTOF* and *FAM89A*, *IFIT1* and *UPB1*, *EIF2AK2* and *FAM89A*, *RSAD2* and *UPB1*, *IFIT3* and *EBI3*, *SLPI* and *IFIT2*, *SLPI* and *IFIT3*, *EMR1* and *IFIT2*, *HS.386275* and *EBI3*, *HS.386275* and *UPB1*, *IFIT3* and *UPB1*, *HS.386275* and *UPB1*, *IFIT3* and *UPB1*, *HS.386275* and *SLPI*, *FAM89A* and *IFI6*, *SLPI* and *IFI27*, *PTPN20* and *IFI44L*, *OTOF* and *UPB1*, *HS.386275* and *S100P*, *S100P* and *IFI27*, *EIF2AK2* and *UPB1*, *EBI3* and *IFI27*, *IFI44L* and *KCNMA1*, *TMEM119* and *EPSTI1*, *IFIT2* and *TMEM119*, *SLPI* and *IFI6*, *IFIT3* and *TMEM119*, *UPB1* and *EPSTI1*, *IFIT1* and *EBI3*, *RSAD2* and *PTPN20*, *EBI3* and *IFIT3*, *IFI44L* and *MERTK*, *EBI3* and *IFI6*, *PI3* and *IFI27*, *IFI2* and *UPB1*, *HS.386275* and *TMEM119*, *IFIT2* and *EBI3*, *TMEM119* and *IFIT3*, *IFIT2* and *MERTK*, *EIF2AK2* and *EBI3*, *S100P* and *SERPING1*, *RSAD2* and *MERTK*, *IFIT3* and *MERTK*, *UPB1* and *IFIT3*, *SERPING1* and *FAM89A*, *IFIT3* and *PTPN20*,

KCNMA1 and *EPSTI1*, *IFIT3* and *KCNMA1*, *SERPING1* and *FAM89A*, *OAS1* and *PTPN20*, *PTPN20* and *EPSTI1*, *OTOF* and *KCNMA1*, and *PTPN20* and *IFIT3*.

6. The method according to any one of the preceding claims, wherein the gene signature comprises at least:
 - a) *IFI44L* and *FAM89A*, and/or
 - b) *OAS1* and *EMR1*, and/or
 - c) *IFI44L* and *IFI27*, and/or
 - d) *IFI44L* and *FAM89A*, and/or
 - e) *OAS1* and *EMR1*, and/or
 - f) *IFI44L* and *IFI27*
7. The method according to any one of the preceding claims, wherein the gene expression levels of one or more of the genes selected from the group consisting of *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3* are upregulated in a subject having a bacterial infection.
8. The method according to any one of the preceding claims, wherein the gene expression levels of one or more of the genes selected from the group consisting of *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *SERPING1*, *OAS1*, *IFI6*, *HLA-DRB6*, *HBZ*, *HS.386275*, *EIF2AK2*, *IFIT1L*, *FCER1A*, *C21ORF7*, *GYPE*, *GYPB*, *HBM*, *EIF1AY*, *LOC649143*, *HBD* and *FBXO7* and are downregulated in a subject having a bacterial infection.
9. The method according to any one of the preceding claims, wherein the method incorporates one or more, such as 1, 2, 3, 4 or 5 housekeeping genes.
10. The method according to any one of the preceding claims, wherein the bacterial infection is selected from the group consisting of: *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Chlamydophila psittaci*, *Mycoplasma pneumonia*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium perfringens*, *Clostridium tetani*, *Enterococcus faecalis*, *Enterococcus faecium*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, Group B streptococcus, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or acid fast bacteria such as *Mycobacterium leprae*, *Mycobacterium tuberculosis*, *Mycobacterium ulcerans*, *mycobacterium avium intercellularae*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Brucella abortus*, *Brucella canis*, *Brucella melitensis*, *Brucella suis*, *Campylobacter jejuni*, *Escherichia coli*, *Francisella tularensis*, *Haemophilus influenzae*, *Helicobacter pylori*, *Legionella pneumophila*, *Leptospira interrogans*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Pseudomonas spp*, *Rickettsia rickettsii*, *Salmonella typhi*, *Salmonella typhimurium*, *Shigella sonnei*, *Treponema pallidum*, *Vibrio cholerae*, *Yersinia pestis*, *Kingella kingae*, *Stenotrophomonas* and *Klebsiella*.
11. The method according to any one of the preceding claims, wherein a subject with bacterial infection can be identified in the presence of viral infection and/or an inflammatory disease.
12. The method according to any one of claims 1 to 11, wherein a subject with bacterial infection can be discriminated from a patient with viral infection and/or inflammatory disease only.

13. The method according to any one of the preceding claims, wherein the subject is a child, for example where the child is in the age range 2 to 59 months.
14. The method according to any one of claims 1 to 13, wherein the subject is an infant in the age range 0 to 59 days.
15. The method according to any one of the preceding claims, wherein the subject has a fever.
16. The method according to any one of the preceding claims wherein the analysis of gene expression modulation employs a microarray.
17. The method according to any one of claims 1 to 16, wherein the analysis gene expression modulation employs: PCR, such as RT-PCR.
18. The method according to claim 16, wherein the PCR is a multiplex PCR.
19. The method according to claim 16 or 17, wherein the PCR is quantitative.
20. The method according to any one of claims 17 to 19, wherein primers employed in the PCR comprise a label or a combination of labels, for example wherein the label is fluorescent or coloured, for example coloured beads.
21. The method according to any one of the preceding claims, which comprises the further step of prescribing a treatment for the subject based on the results of the analysis of said gene signature.
22. A set of primers for use in multiplex PCR wherein the set of primers includes nucleic acid sequences specific to a polynucleotide gene transcript for at least one gene from the group consisting of:
 - a) *IFI44L*, *IFI27*, *IFIT1*, *RSAD2*, *IFIT3*, *OTOF*, *IFIT2*, *EPSTI1*, *OAS1*, *IFI6*, *HS.386275* and *EIF2AK2*; and optionally includes nucleic acid sequences specific to a polynucleotide gene transcript for one or more genes selected from the group consisting of:
 - b) *FAM89A*, *KCNMA1*, *MERTK*, *EBI3*, *UPB1*, *EMR1*, *PTPN20*, *TMEM119*, *SLPI*, *S100P* and *PI3*.
23. The set of primers according to claim 22, wherein the nucleic acid sequences in the set are for no more than a total of 10 genes, for example no more than 5 genes, such as 2, 3, 4, or 5 genes.
24. The set of primers according to claim 22 or 23 wherein the set of primers includes one or more nucleic acids sequences specific to a gene transcript encoding:
 - a) *IFI44L*, for example the *IFI44L* sequence shown in SEQ ID NO: 1 and/or
 - b) *FAM89A*, for example the *FAM89A* sequence shown in SEQ ID NO: 2.
25. The set of primers according to any one of claims 22 to 24 wherein the primer length is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 or 100 bases in length.
26. The set of primers according to any one of claims 22 to 25, wherein the primers comprise or consist of the sequences given in any one of SEQ ID NOs: 3 to 40.
27. A point of care test for identifying bacterial infection in a subject comprising the set of primers defined in any one of claims 22 to 26.
28. Use of the set of primers defined in any one of claims 27 to 32 in an assay to detect bacterial infection in a sample, for example a blood sample.

Figure 1



*Controls not used for signature discovery

Figure 1

B

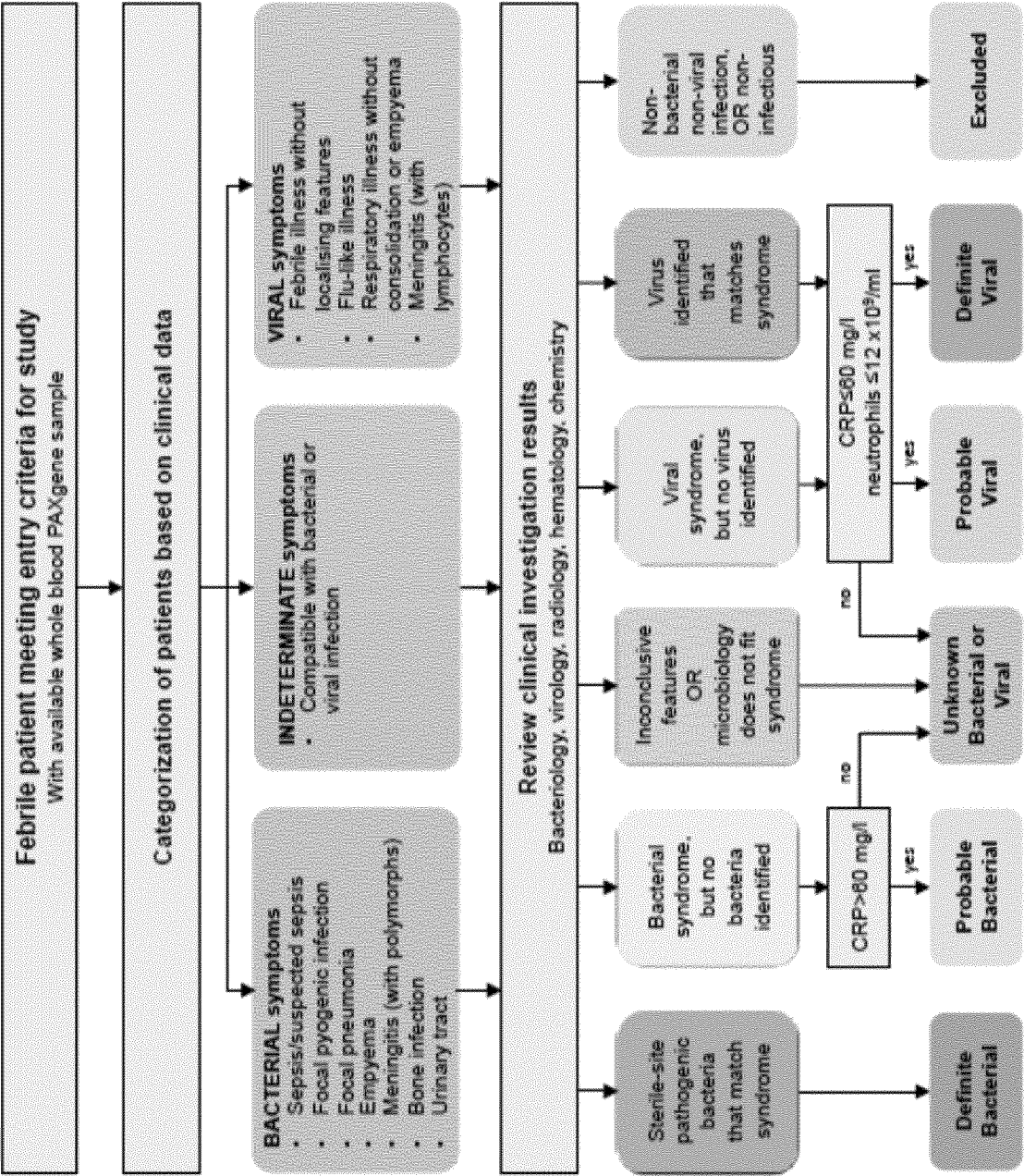


Figure 2

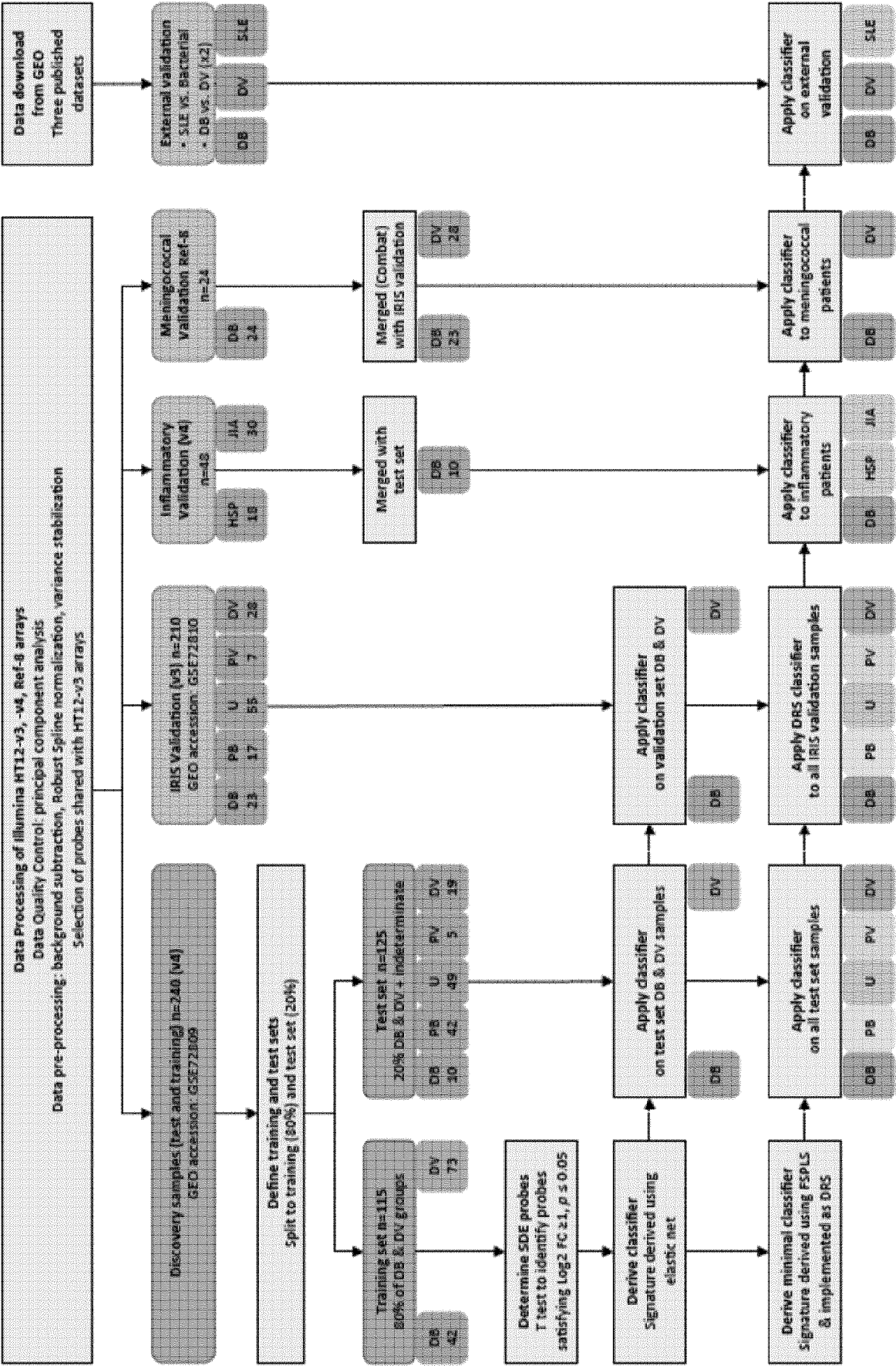


Figure 3

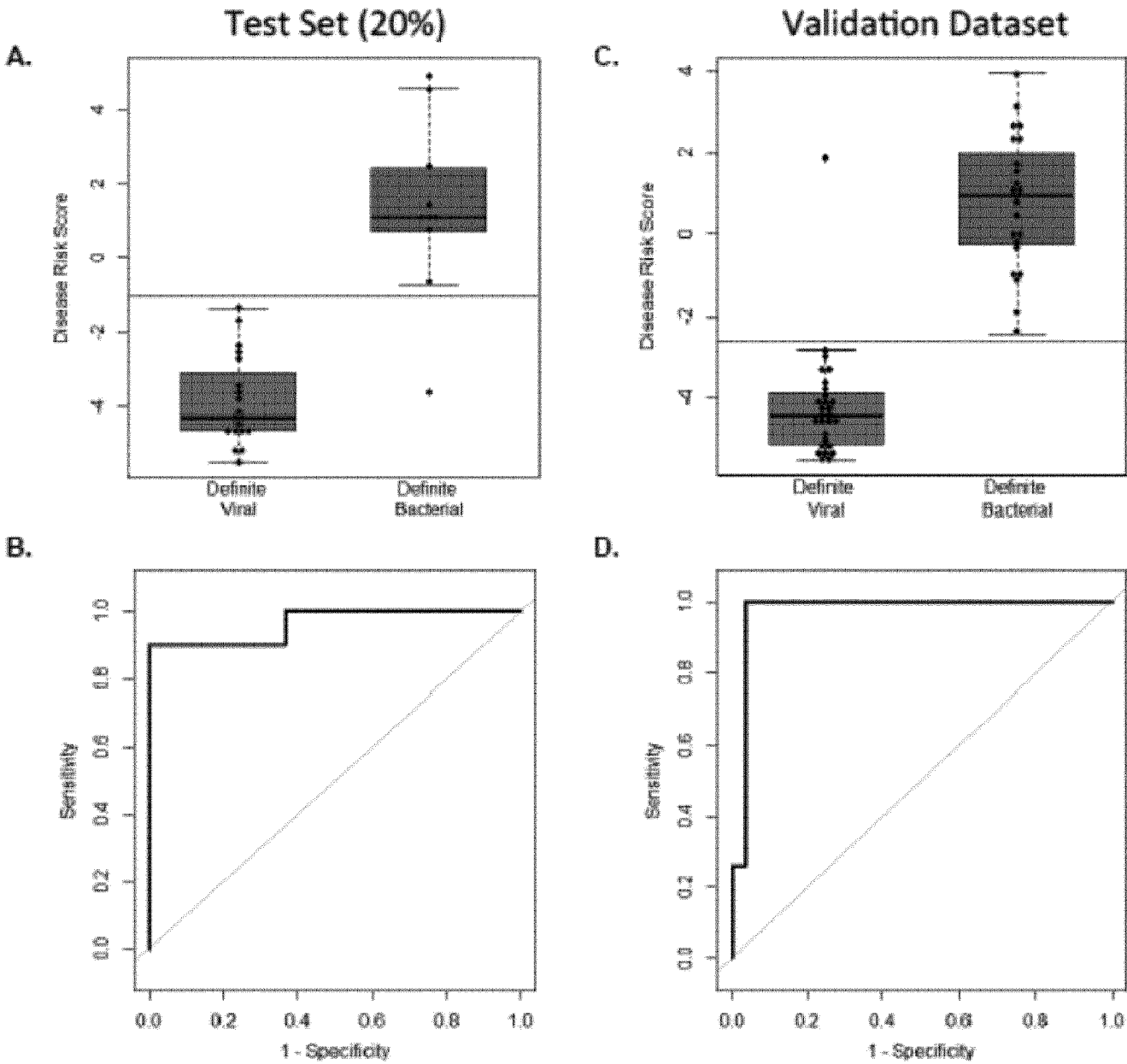


Figure 4

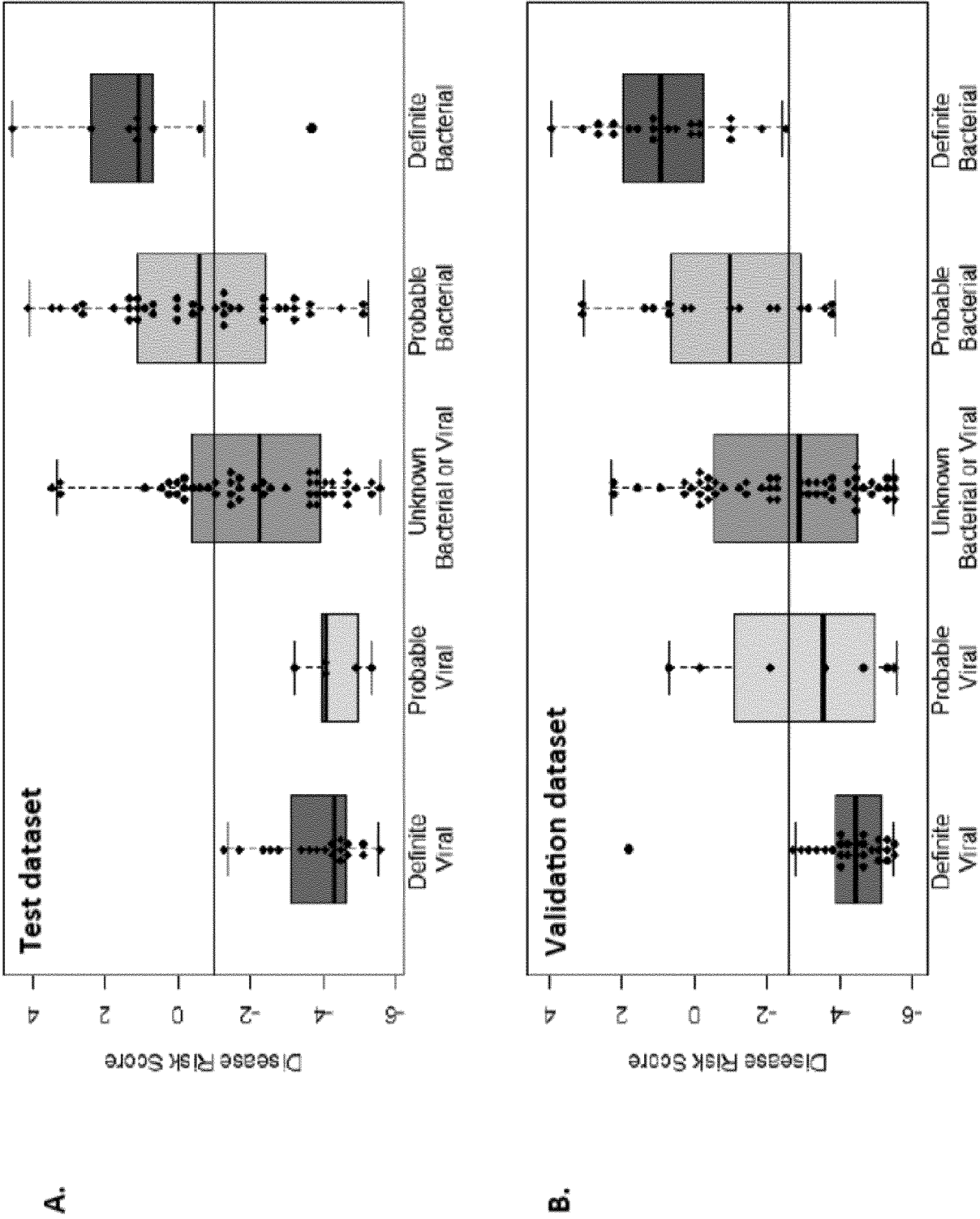
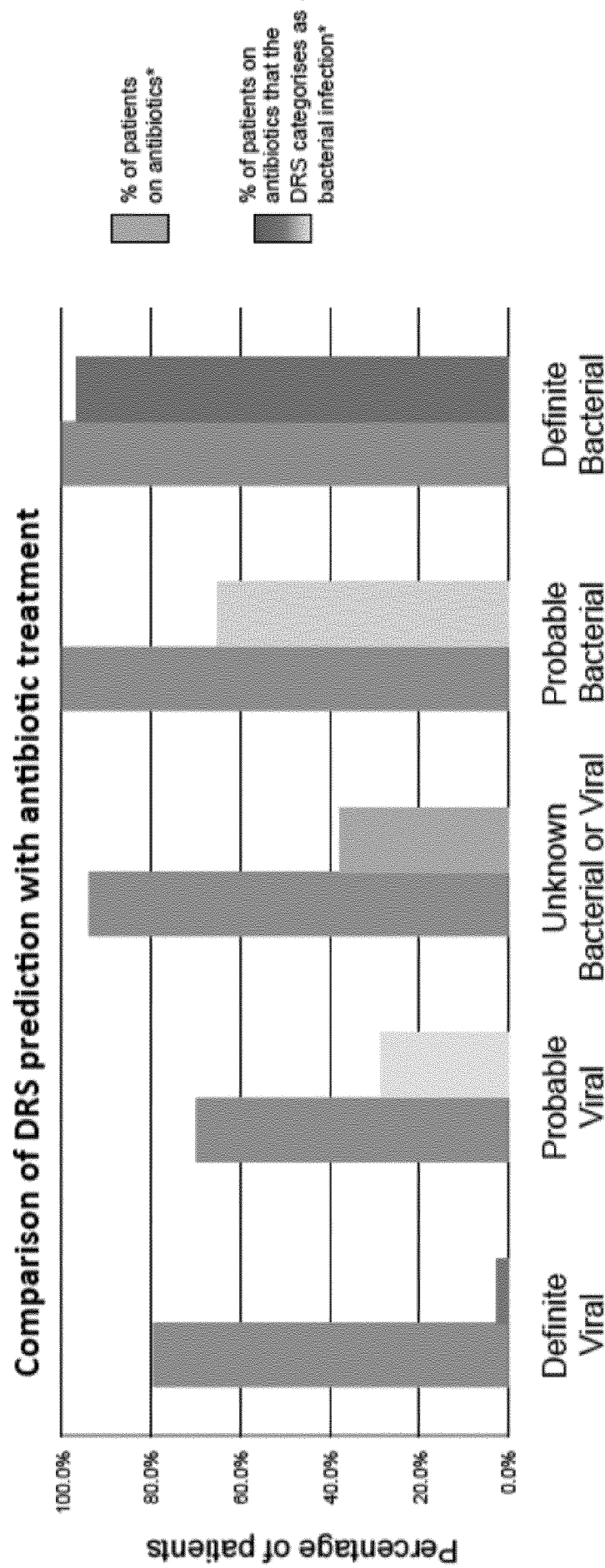


Figure 5



	Definite Viral	Probable Viral	Unknown Bacterial or Viral	Probable Bacterial	Definite Bacterial
n _{total}	39	10	77	49	28
n _{antibiotics}	33	7	73	49	28
n _{bacterial DRS}	1	2	29	32	27

Figure 6

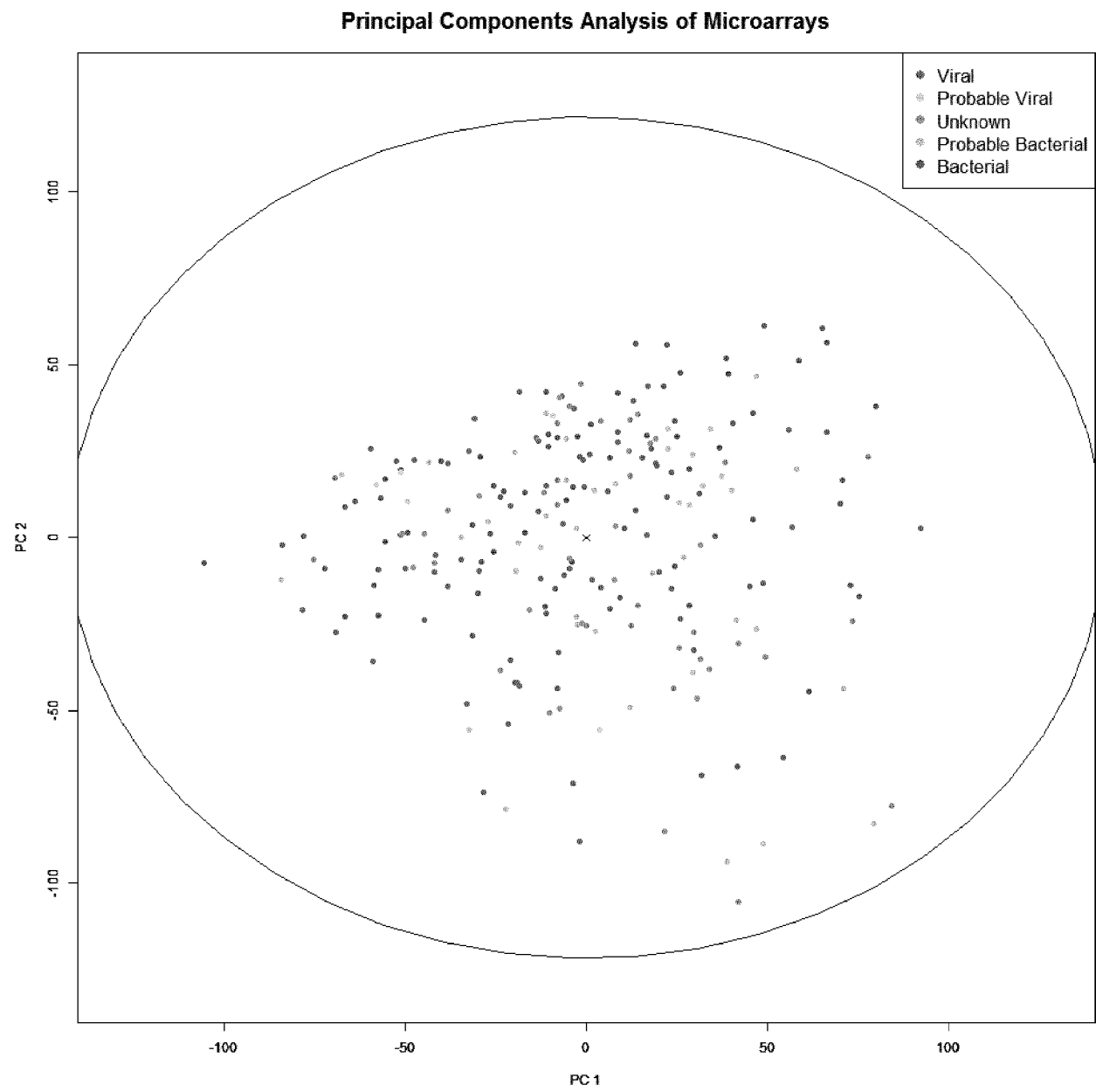


Figure 7A

Training Set

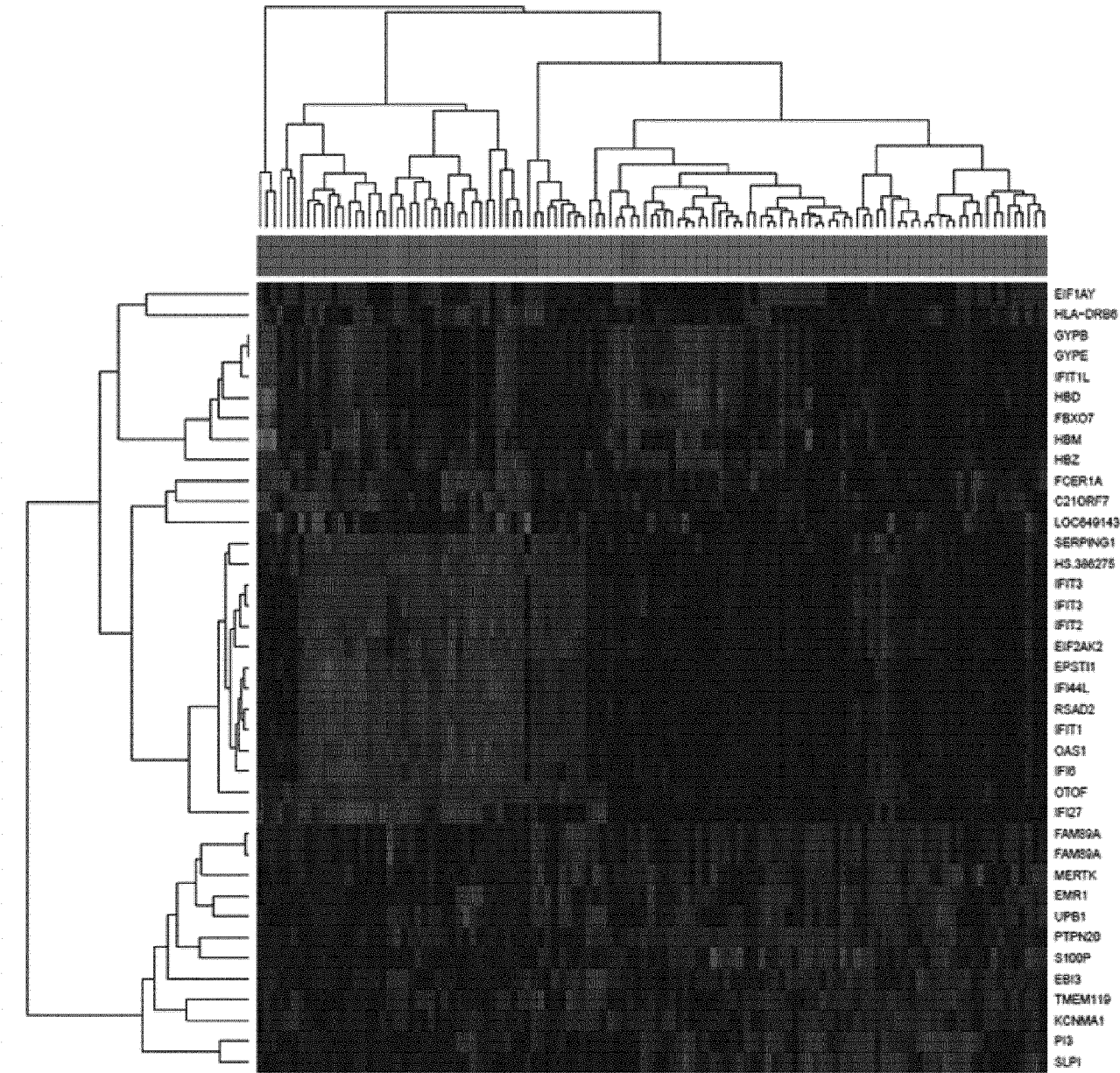
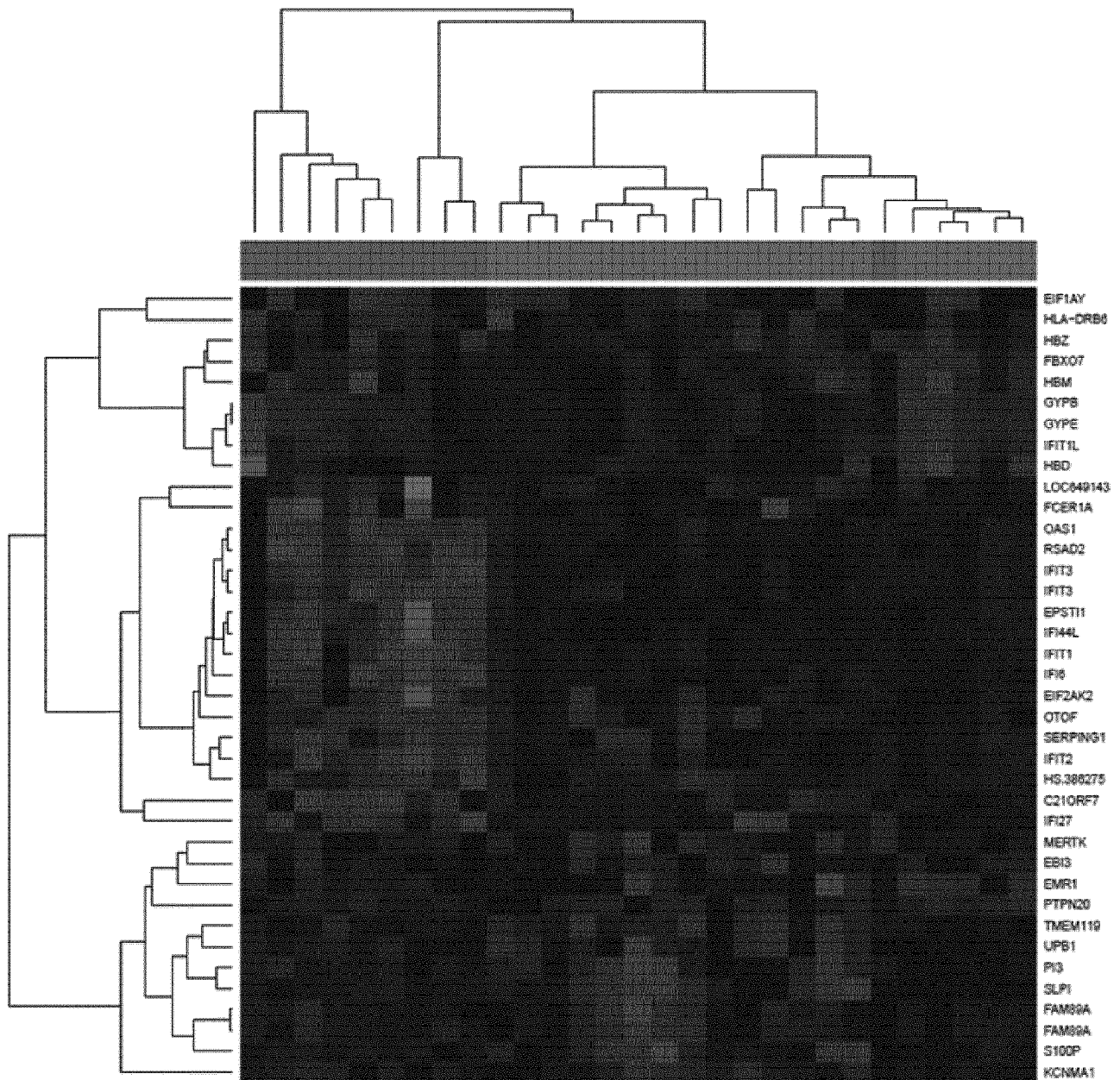


Figure 7B

Test Set



10/24

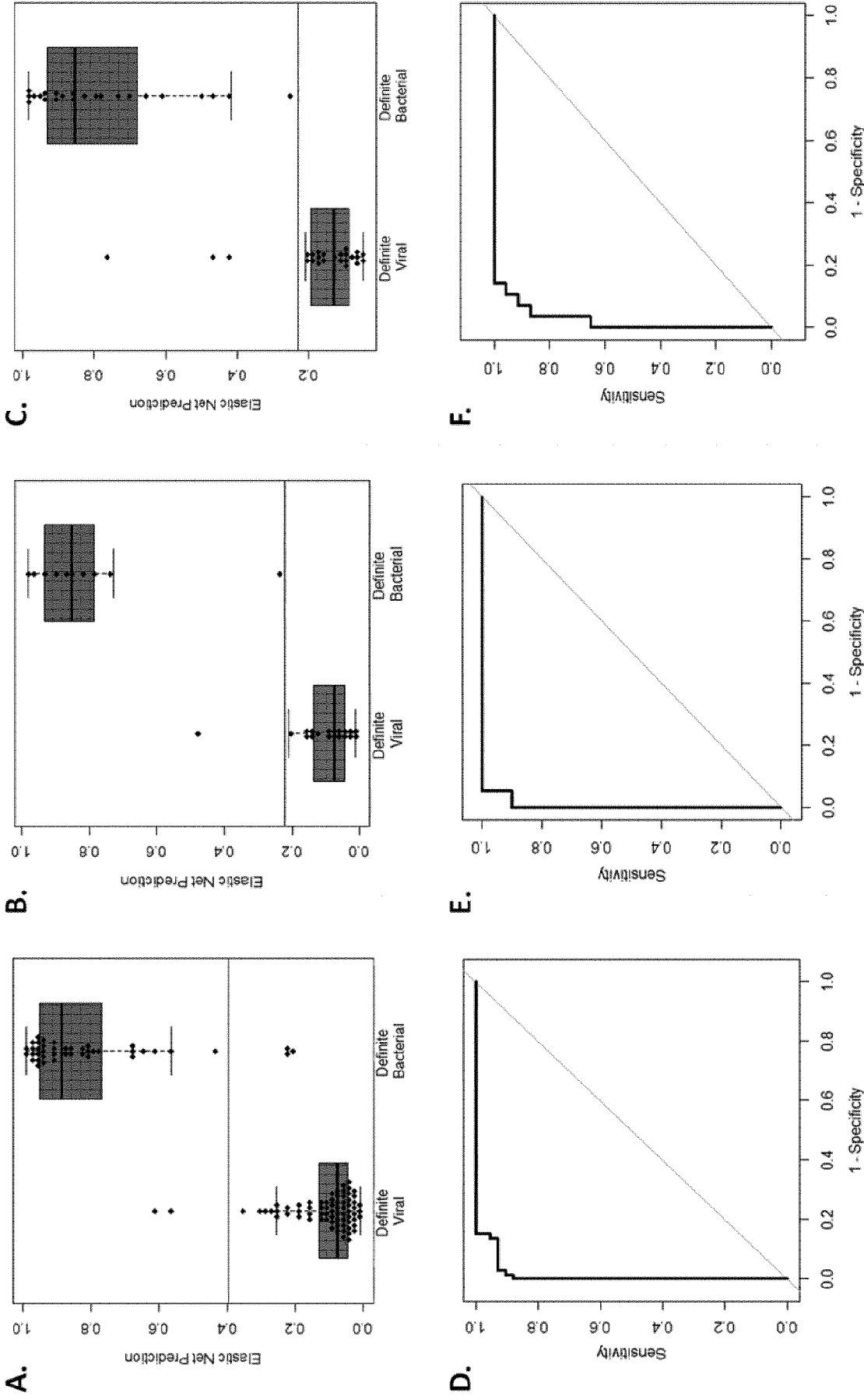


Figure 8

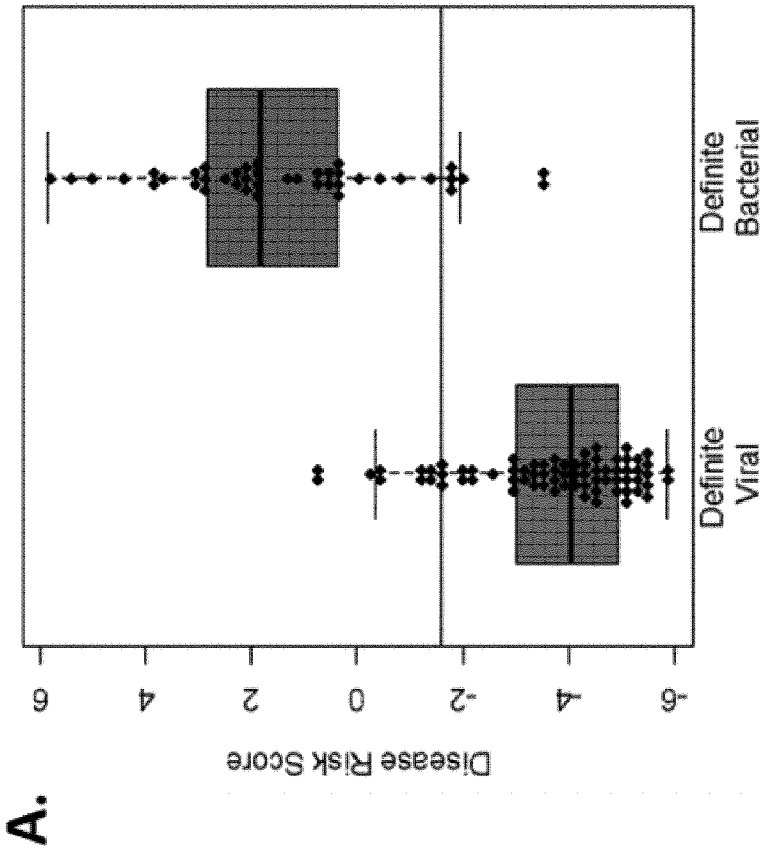
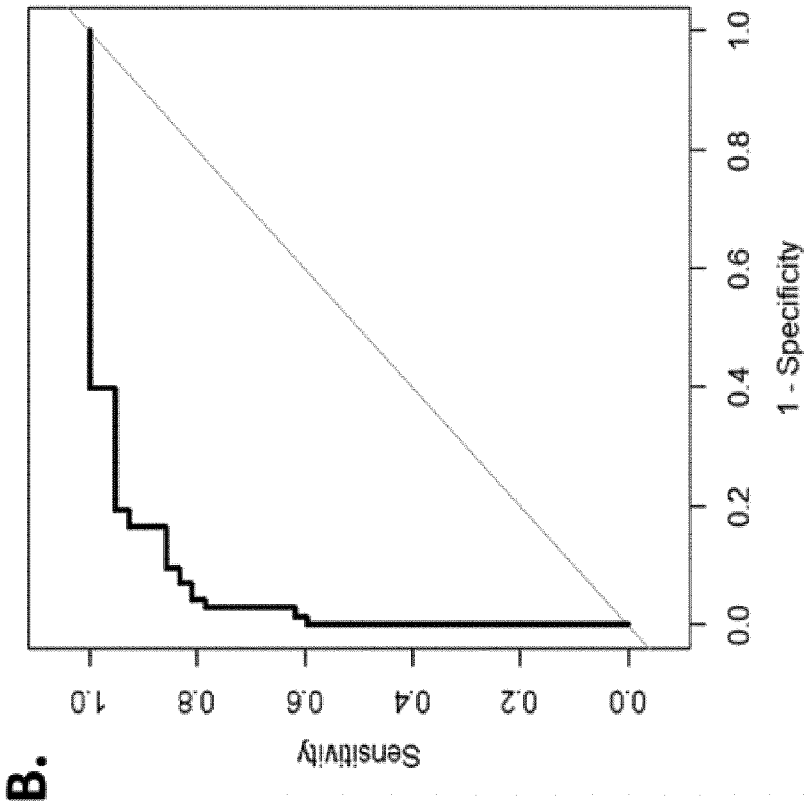


Figure 9

```

graph TD
    A[Eligible discovery participants with febrile illness and microarray data  
n=240] --> B[Participants with DRS (index test) result to be compared with clinical phenotyping in the test set  
n=125]
    A --> C[Excluded n= 115  
Used for training set]
    B --> D[Participants with bacterial]
    B --> E[Index test negative: participants with DRS predicted viral  
n=78]
    D --> F[No reference standard: clinical coding as uncertain (PB, U or PV)  
n=38]
    E --> G[No reference standard: clinical coding as uncertain (PB, U or PV)  
n=58]
    E --> H[Reference standard: coded as DB/DV  
n=20]
    H --> I[Final diagnosis  
Target condition present (DV) n=19  
Target condition absent (DB) n=1]
    I --> J[Table]
  
```

Eligible discovery participants with febrile illness and microarray data
n=240

Excluded n= 115
Used for training set

Participants with DRS (index test) result to be compared with clinical phenotyping in the test set
n=125

Participants with bacterial

No reference standard: clinical coding as uncertain (PB, U or PV)
n=38

No reference standard: clinical coding as uncertain (PB, U or PV)
n=58

Reference standard: coded as DB/DV
n=20

Final diagnosis
Target condition present (DV) n=19
Target condition absent (DB) n=1

	Clinical coding DB	Clinical coding DV
DRS predicted bacterial	9	0
DRS predicted viral	1	19

Figure 10

B

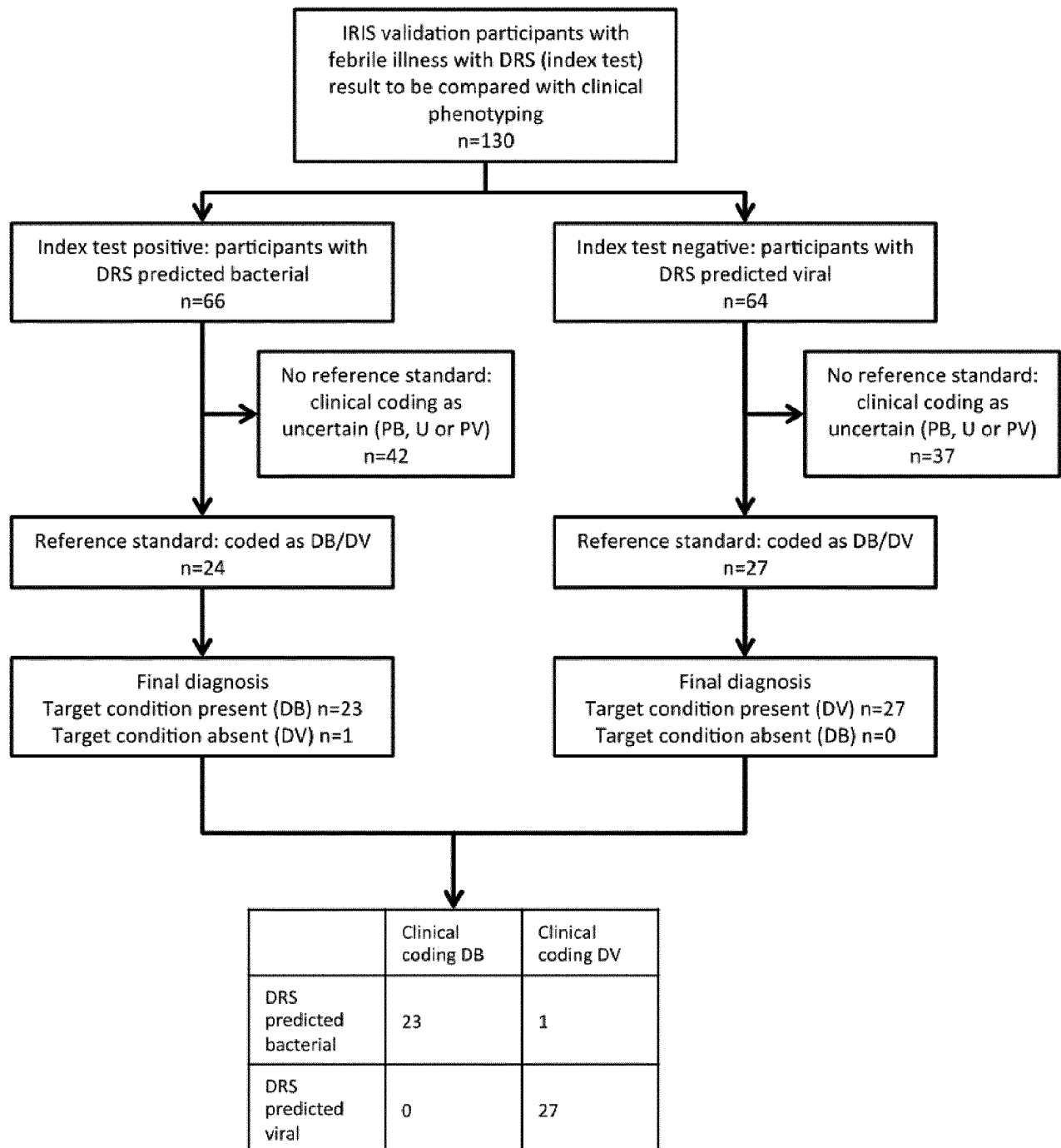
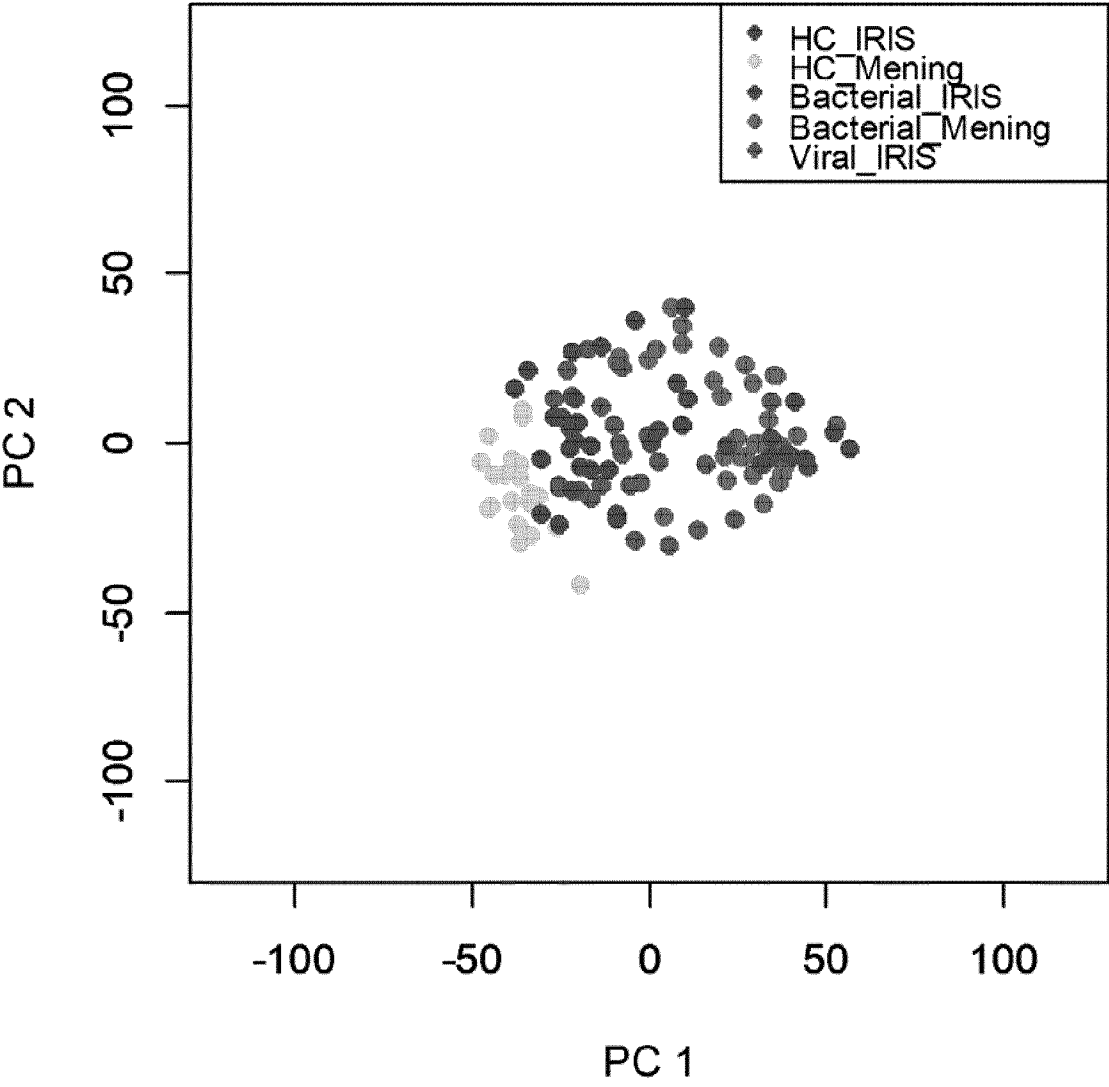


Figure 11



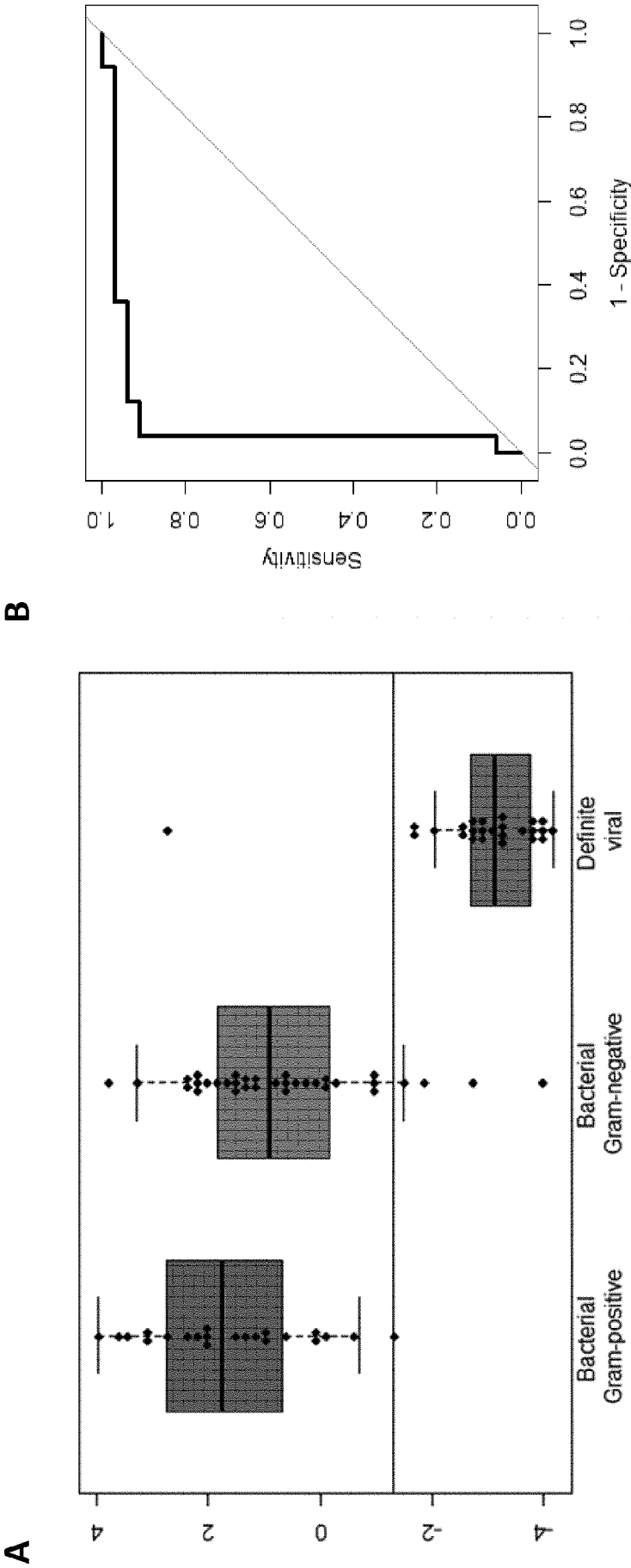


Figure 12

Figure 13

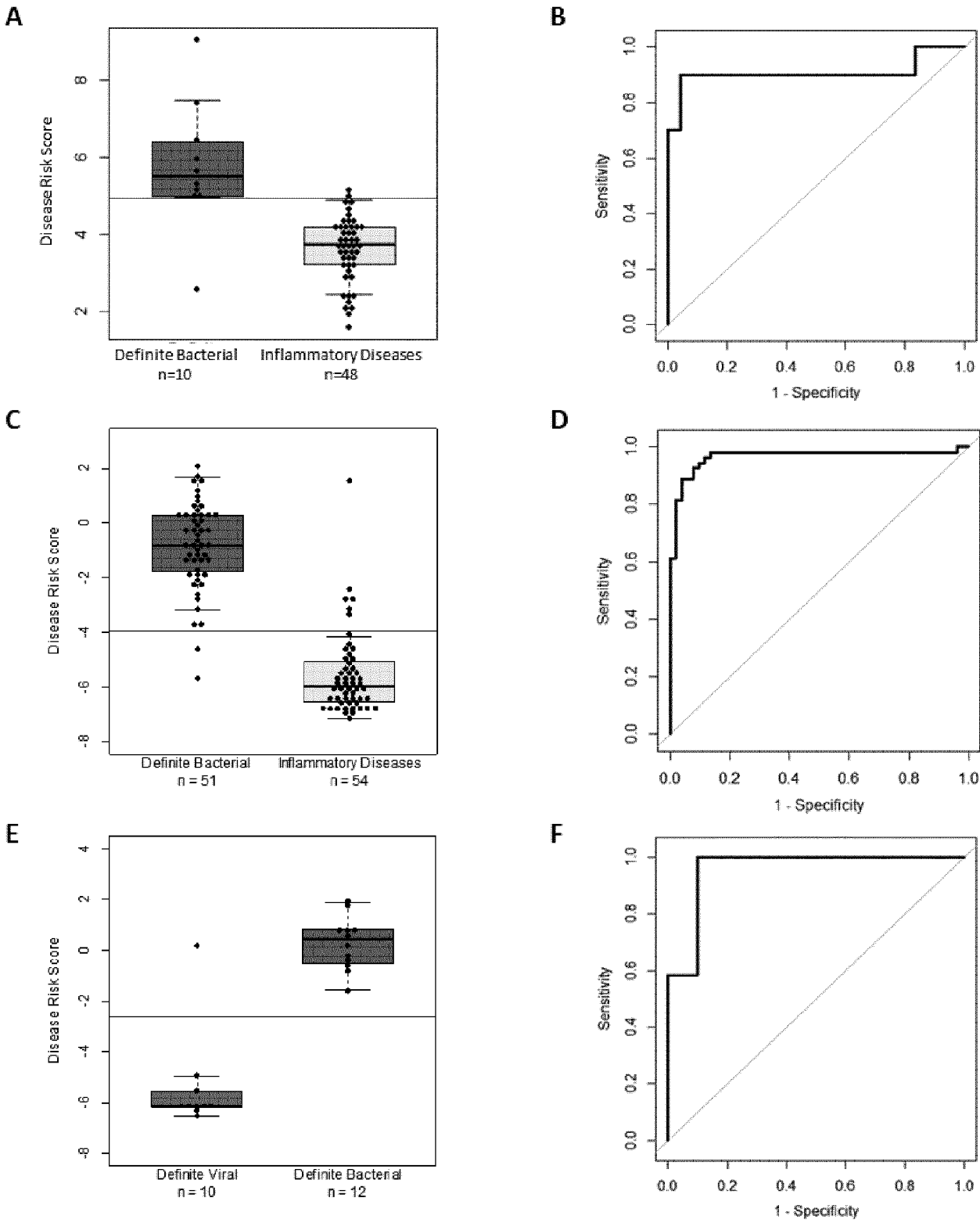


Figure 13

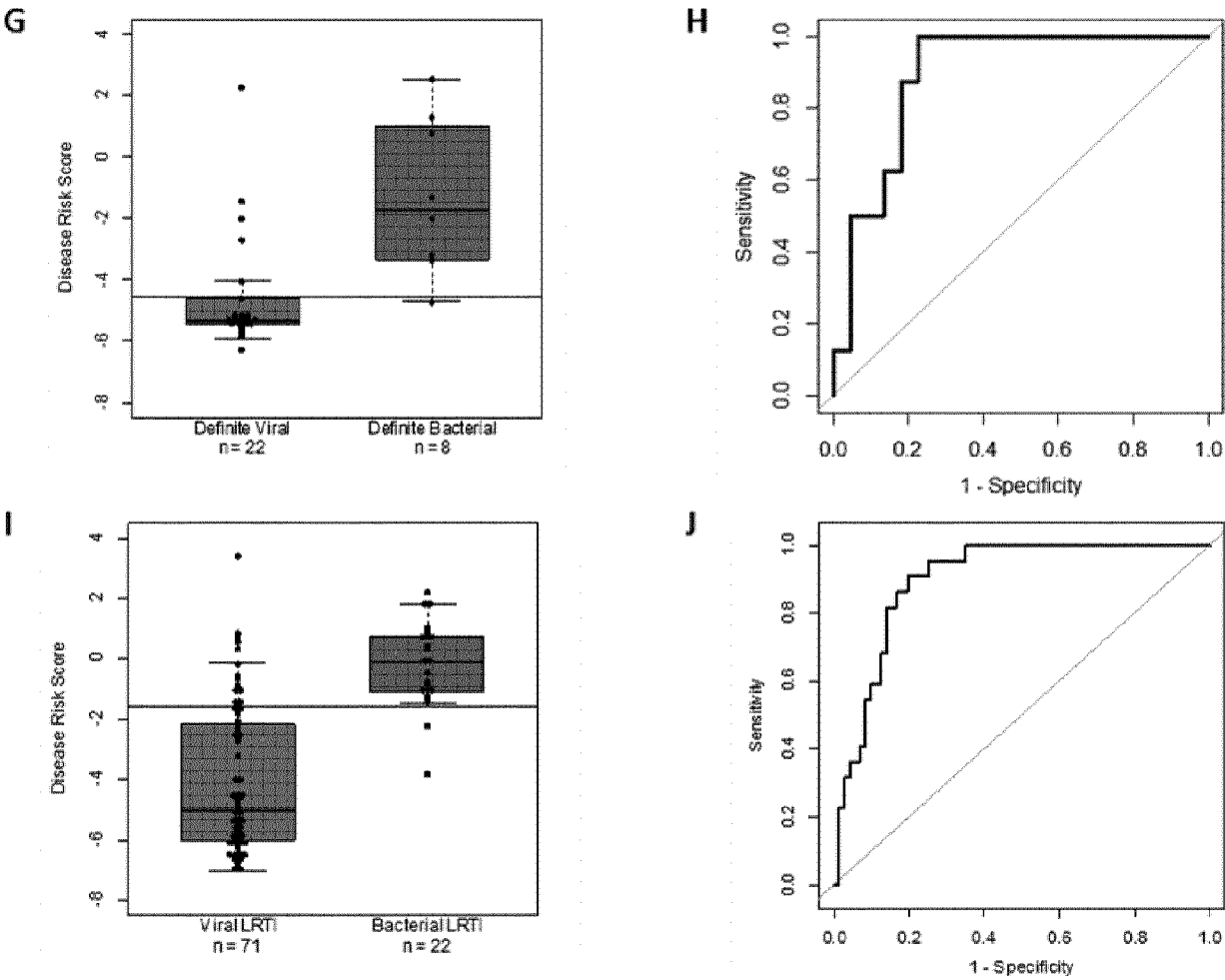
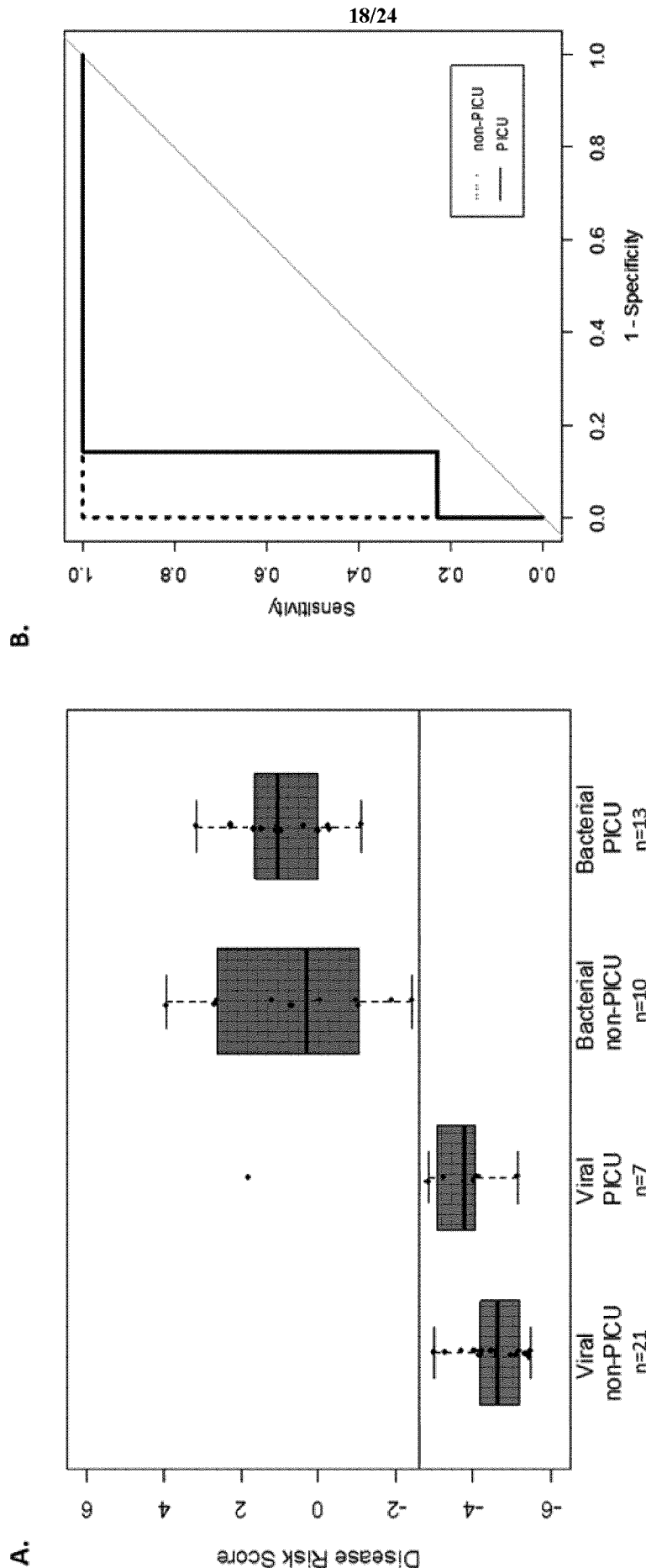


Figure 14



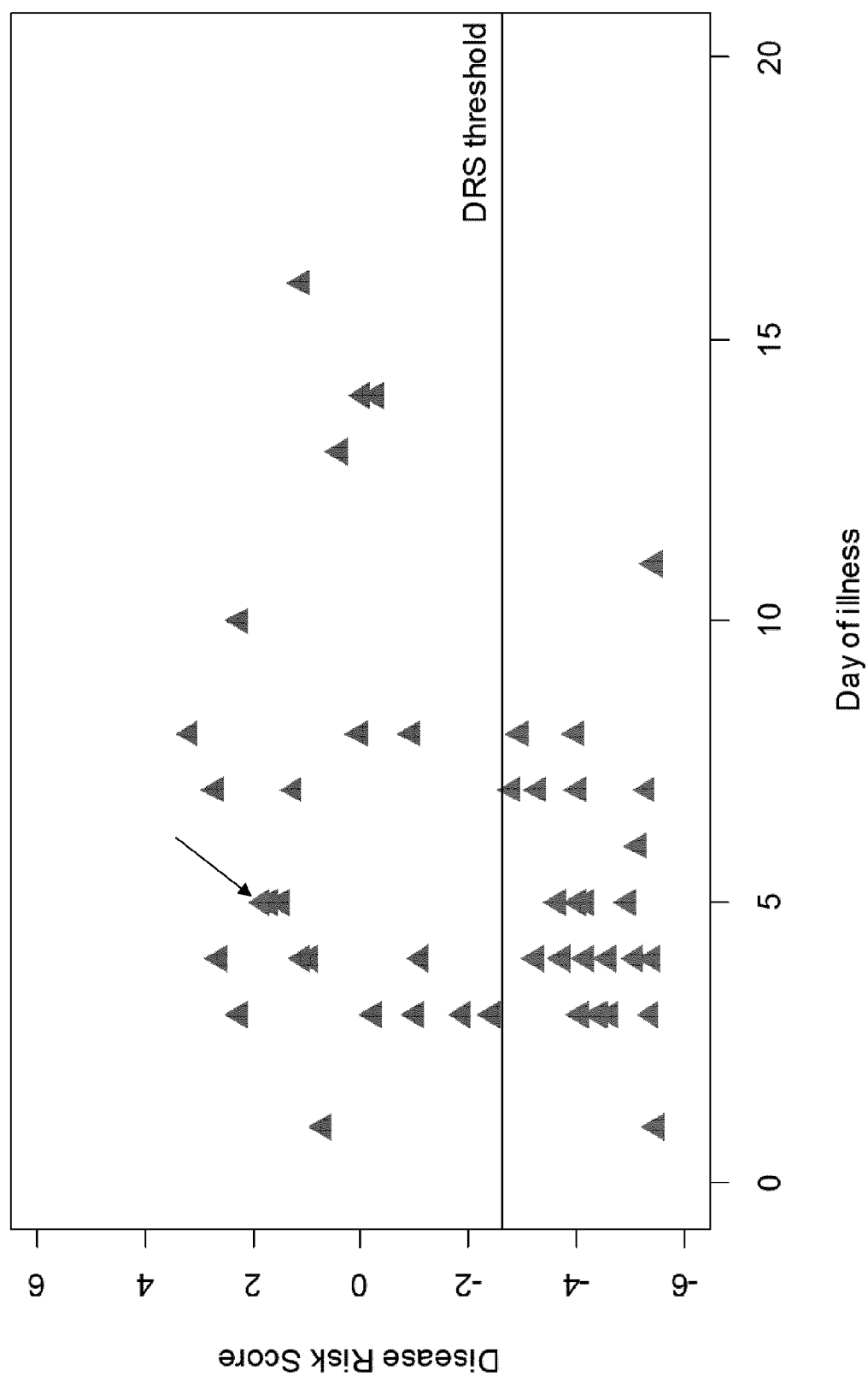


Figure 15

Figure 16A

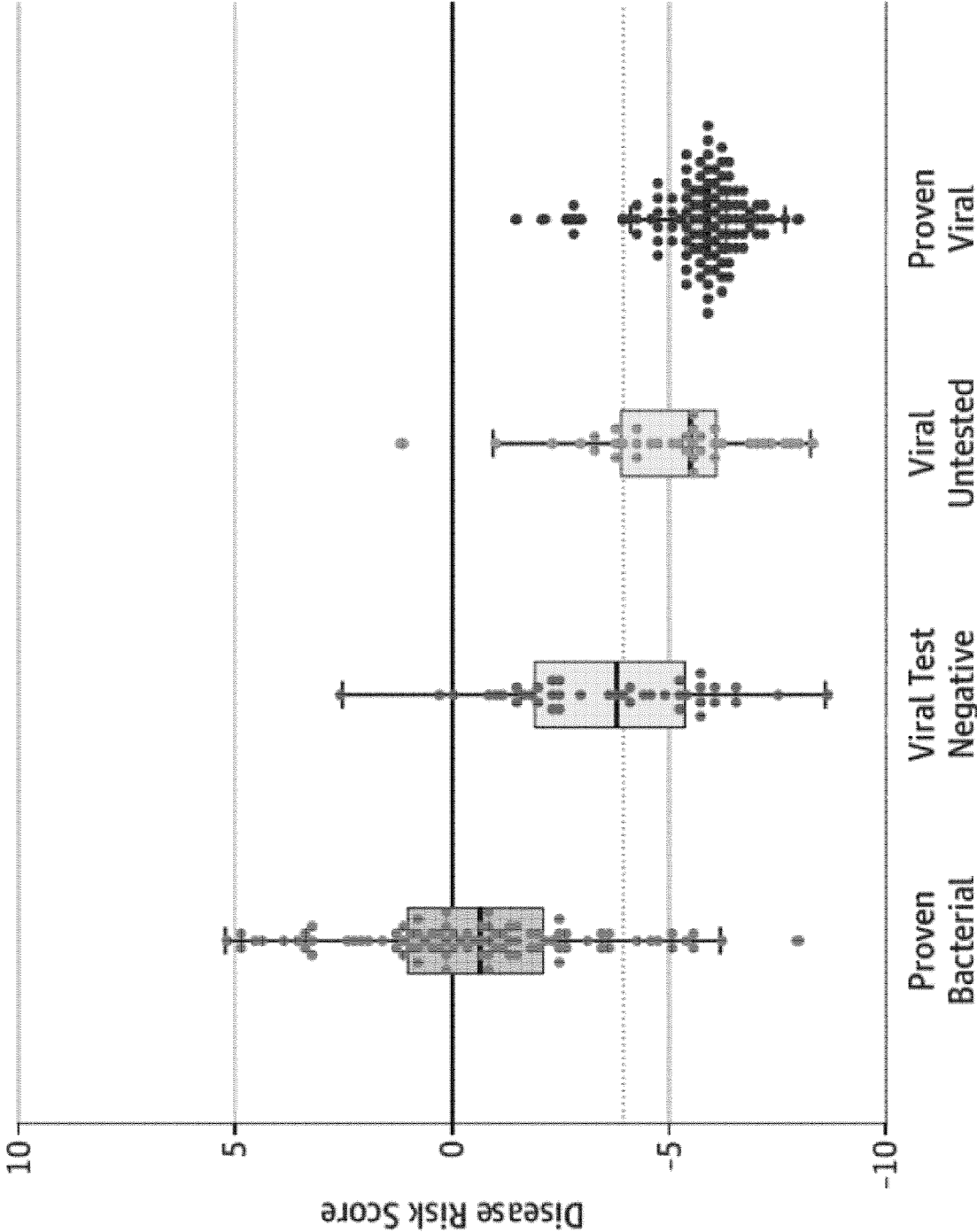
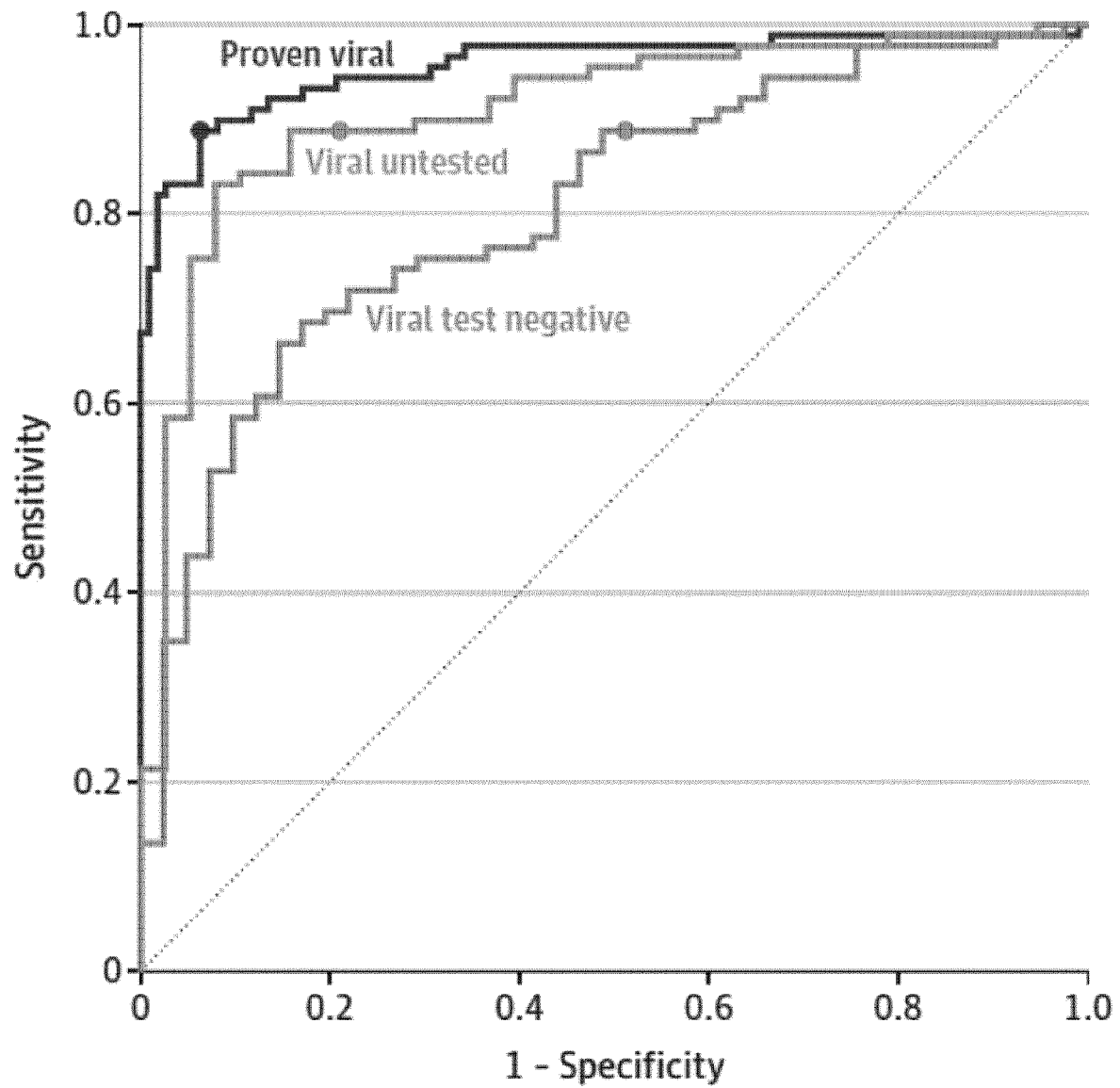


Figure 16B



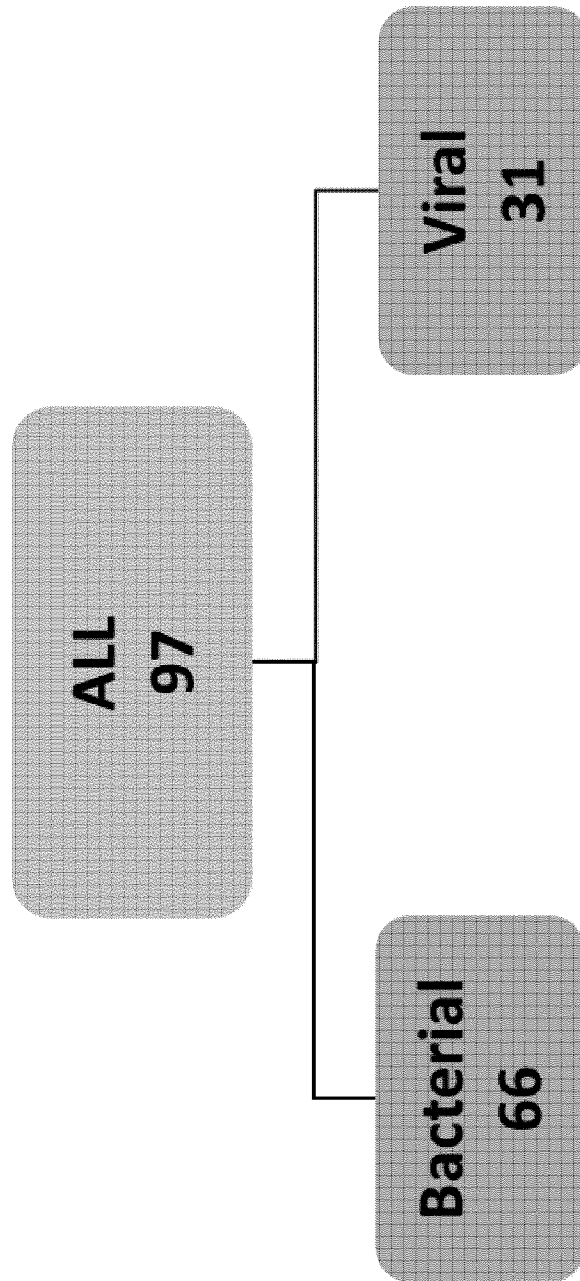


Figure 17A

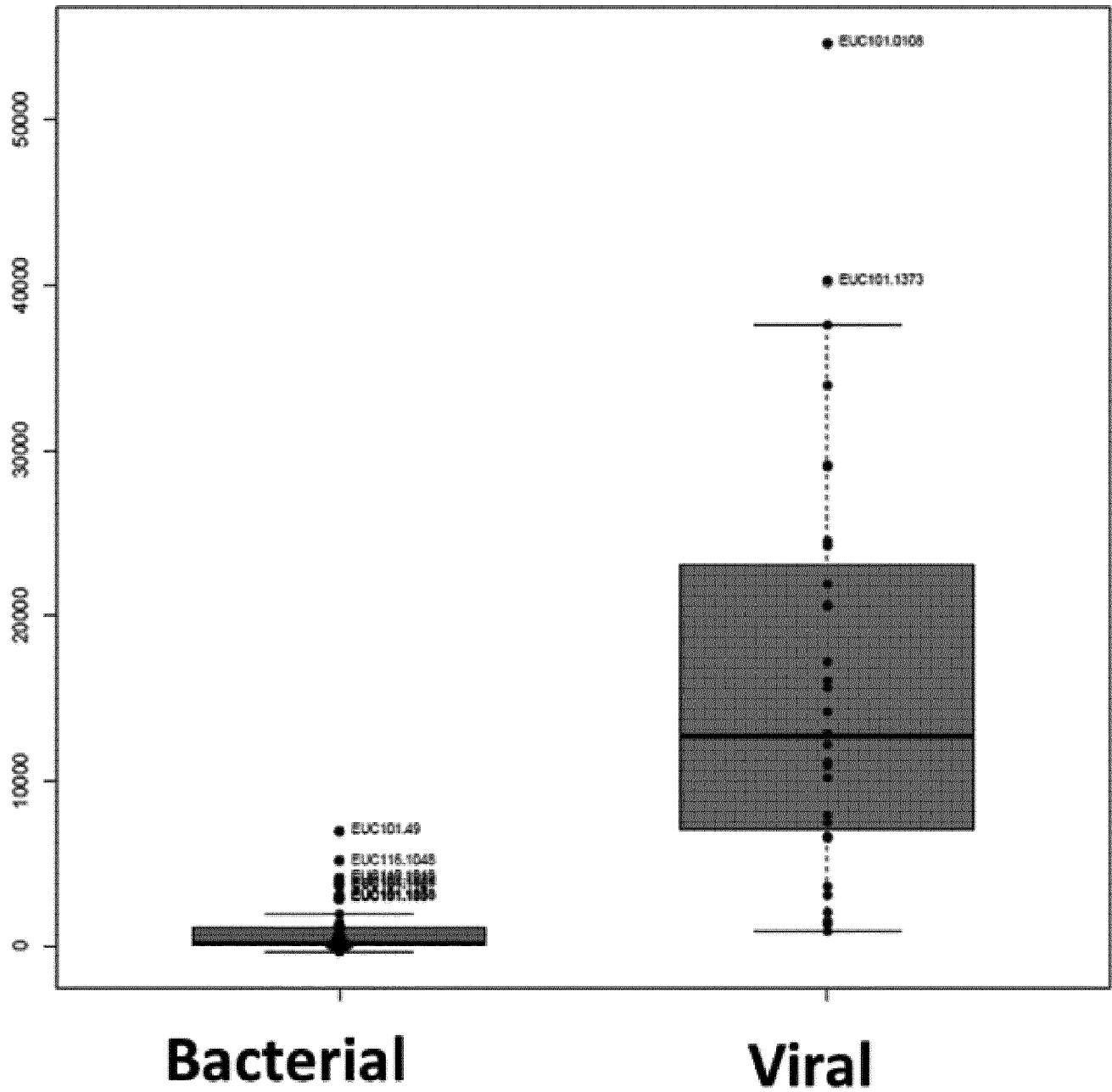
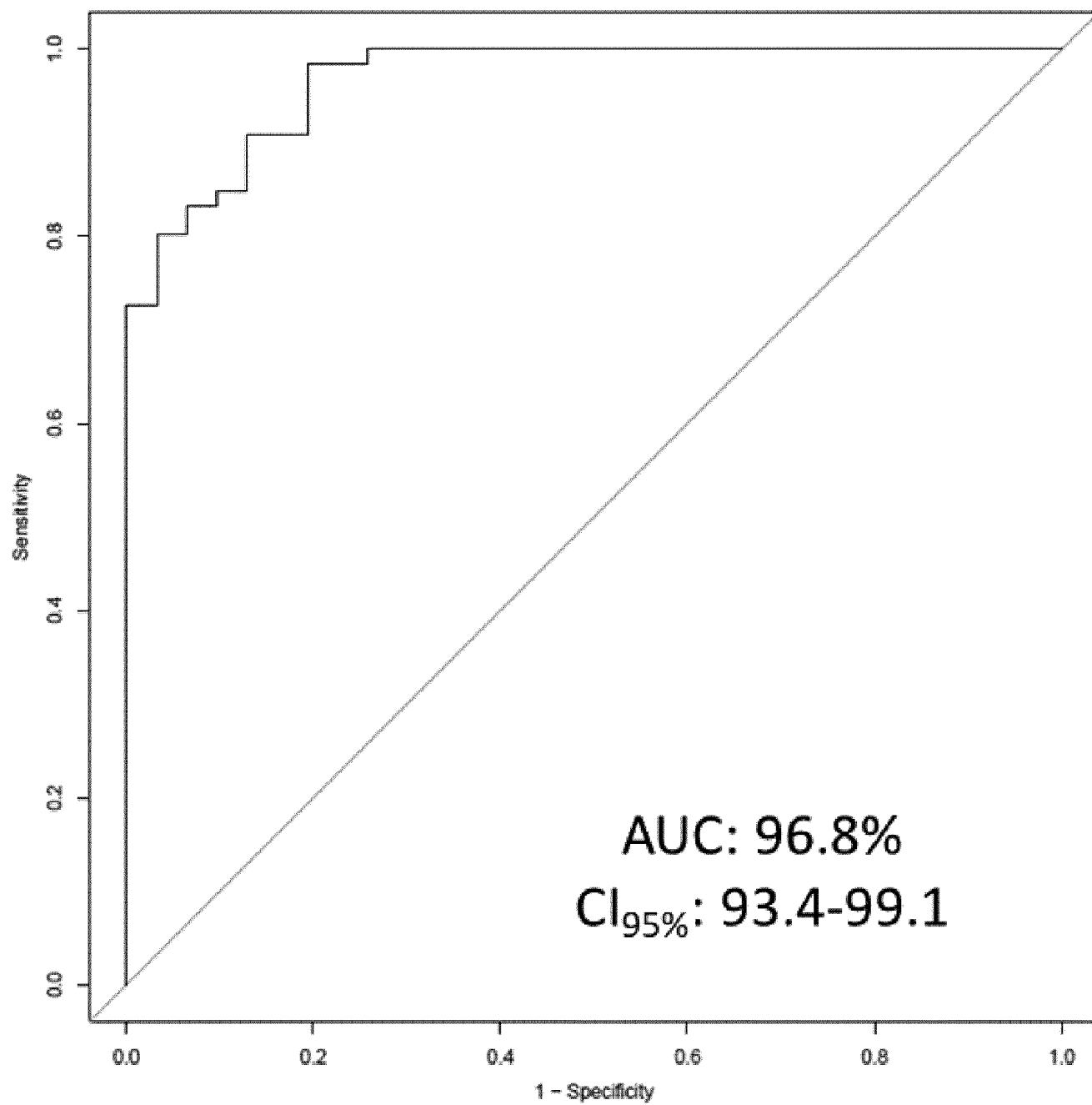
Figure 17B

Figure 17C

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/067637

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

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)
C12Q

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

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

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 2014/019977 A1 (IMP INNOVATIONS LTD [GB]) 6 February 2014 (2014-02-06) abstract example 1 claims 1,5,10 -----	1-21 22-28
X A	WO 2014/067943 A1 (IMP INNOVATIONS LTD [GB]) 8 May 2014 (2014-05-08) abstract claims 1, 10-12 ----- -/--	1-21 22-28



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

6 November 2017

Date of mailing of the international search report

15/11/2017

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Authorized officer

Barz, Wolfgang

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/067637

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Illumina ET AL: "Whole-Genome Expression Analysis Using the Sentrix Human-6 and HumanRef-8 Expression BeadChips", Technical Bulletin, 1 January 2005 (2005-01-01), XP055039149, Retrieved from the Internet: URL:http://www.illumina.com/Documents/products/techbulletins/techbulletin_whole_genome_expression.pdf [retrieved on 2012-09-25] the whole document -----	22-28
X	ILLUMINA ET AL: "Human-6 v2 and HumanRef-8 v2 Expression BeadChips", INTERNET CITATION, 23 December 2006 (2006-12-23), pages 1-4, XP002701086, Retrieved from the Internet: URL:http://www.switchtoi.com/pdf/GXHuman6-8v2Datasheet.pdf [retrieved on 2013-07-09] the whole document -----	22-28
A	WO 2013/114123 A1 (IMP INNOVATION LTD [GB]) 8 August 2013 (2013-08-08) abstract claims 1-2, 5-10 -----	1-28
A	PRASHANT MAHAJAN ET AL: "RNA Transcriptional Biosignature Analysis for Identifying Febrile Infants With Serious Bacterial Infections in the Emergency Department : A Feasibility Study", PEDIATRIC EMERGENCY CARE, vol. 31, no. 1, 1 January 2015 (2015-01-01), pages 1-5, XP055420008, US ISSN: 0749-5161, DOI: 10.1097/PEC.0000000000000324 ----- -/--	1-28

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/067637

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	HERBERG JETHRO A ET AL: "Diagnostic Test Accuracy of a 2-Transcript Host RNA Signature for Discriminating Bacterial vs Viral Infection in Febrile Children", JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, AMERICAN MEDICAL ASSOCIATION, US , vol. 316, no. 8 31 July 2016 (2016-07-31), pages 835-845, XP009500864, ISSN: 0098-7484, DOI: 10.1001/JAMA.2016.11236 Retrieved from the Internet: URL:http://epo.summon.serialssolutions.com/2.0.0/link/0/eLvHCXmwtV1Nb9QwELWokBAXRAuC hVadAwekVaQ4ceLscw1pVyA41KUSp8h0bMh1i7ptpR 77z5nXR5Ju1lQOXKJVsmthw_HM5PxG8bezaxsVdbM Em0txQC10Y10szZpcOnhhmdautTAjw0xPJYnx9StIf beG879V6TxHGJN02f_Ae1-UDyBnxFzPCLqeHwQ7oe- do50WJdo8akdxOU59XR3GyGzxC10z1RQz5CL6cnX-f Rb99MLfLqi the whole document figures 1-5 tables 1-2 Conclusions -----	1-28
X,P	KAFOROU MYRSINI ET AL: "Diagnosis of Bacterial Infection Using a 2-Transcript Host RNA Signature in Febrile Infants 60 Days or Younger", JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, AMERICAN MEDICAL ASSOCIATION, US , vol. 317, no. 15 18 April 2017 (2017-04-18), pages 1577-1578, XP009500866, ISSN: 0098-7484, DOI: 10.1001/JAMA.2017.1365 Retrieved from the Internet: URL:http://epo.summon.serialssolutions.com/2.0.0/link/0/eLvHCXmwtV1LS8QwEA6KIF7EF_iE OXgrlTzt2u1R1xeiHtZF8CRpmmpBdmXRg__emSRt6r IHPXgpuwNbSufbmczkyzeMHZd5mepC8VDVmQjTmNeh VHUCiXxueNIZ0bA9GmYjq_y0RVNa2inZHnbv3oabe hrOjn7B293N0UDfkaf4xw9jtdf-f3ccueszMiZ1WI2 ehqWdDUJLE1ABjw0ecpEDRof8hGM7k-Dh-bFan1SI- QSC2aMGvRj the whole document -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/067637

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014019977 A1	06-02-2014	EP 2880178 A1	10-06-2015
		US 2015203899 A1	23-07-2015
		WO 2014019977 A1	06-02-2014
WO 2014067943 A1	08-05-2014	EP 2914740 A1	09-09-2015
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		WO 2014067943 A1	08-05-2014
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