FIGURE 1

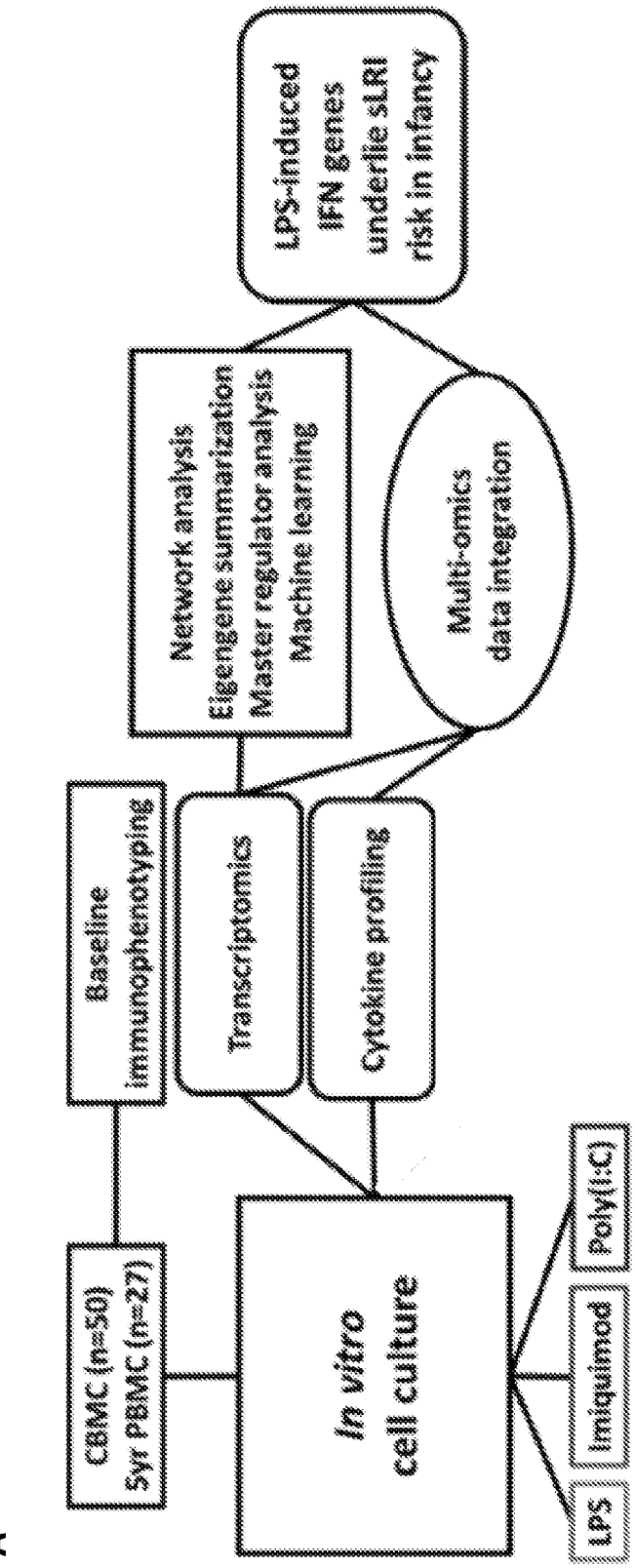

A
CBMC (n=50)
Syr PBMC (n=27)
Baseline immunophenotyping
In vitro cell culture
LPS
Imiquimod
Poly(I:C)
Transcriptomics
Cytokine profiling
Network analysis
Eigengene summarization
Master regulator analysis
Machine learning
Multi-omics data integration
LPS-induced IFN genes underlie sLRI risk in infancy

FIGURE 1 continued

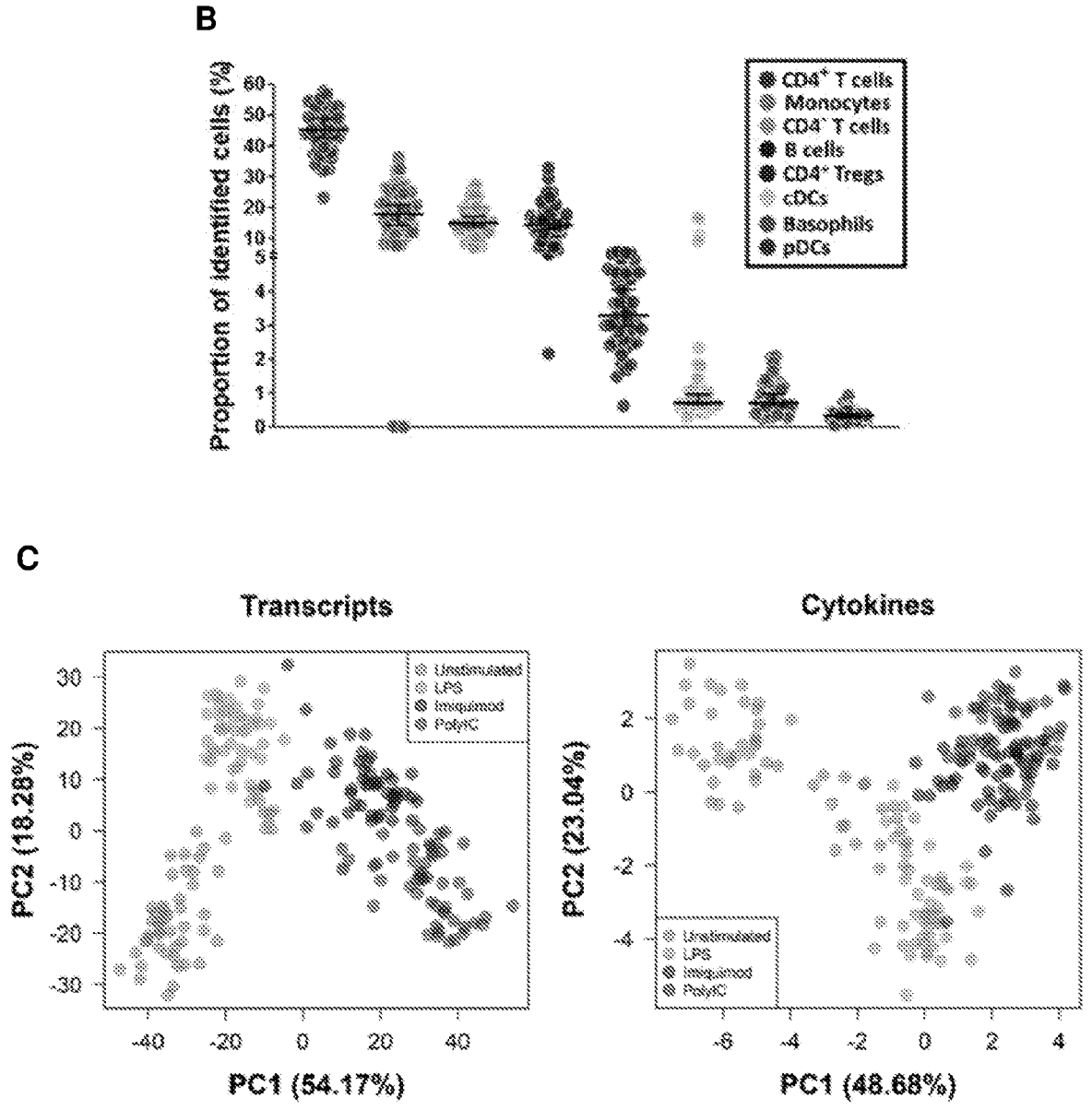
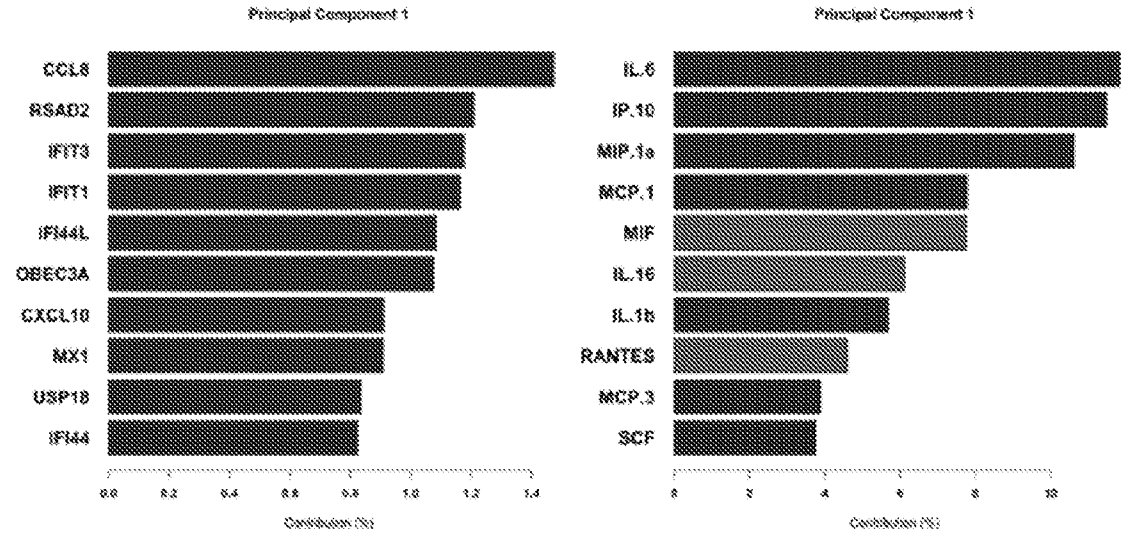


FIGURE 1 continued

D



E

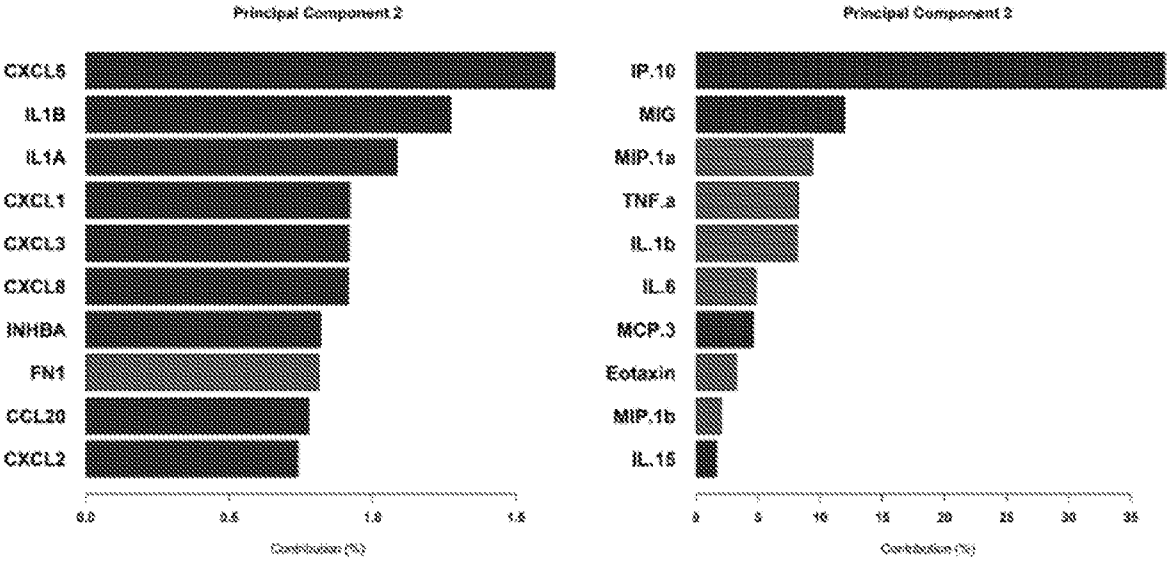


FIGURE 2

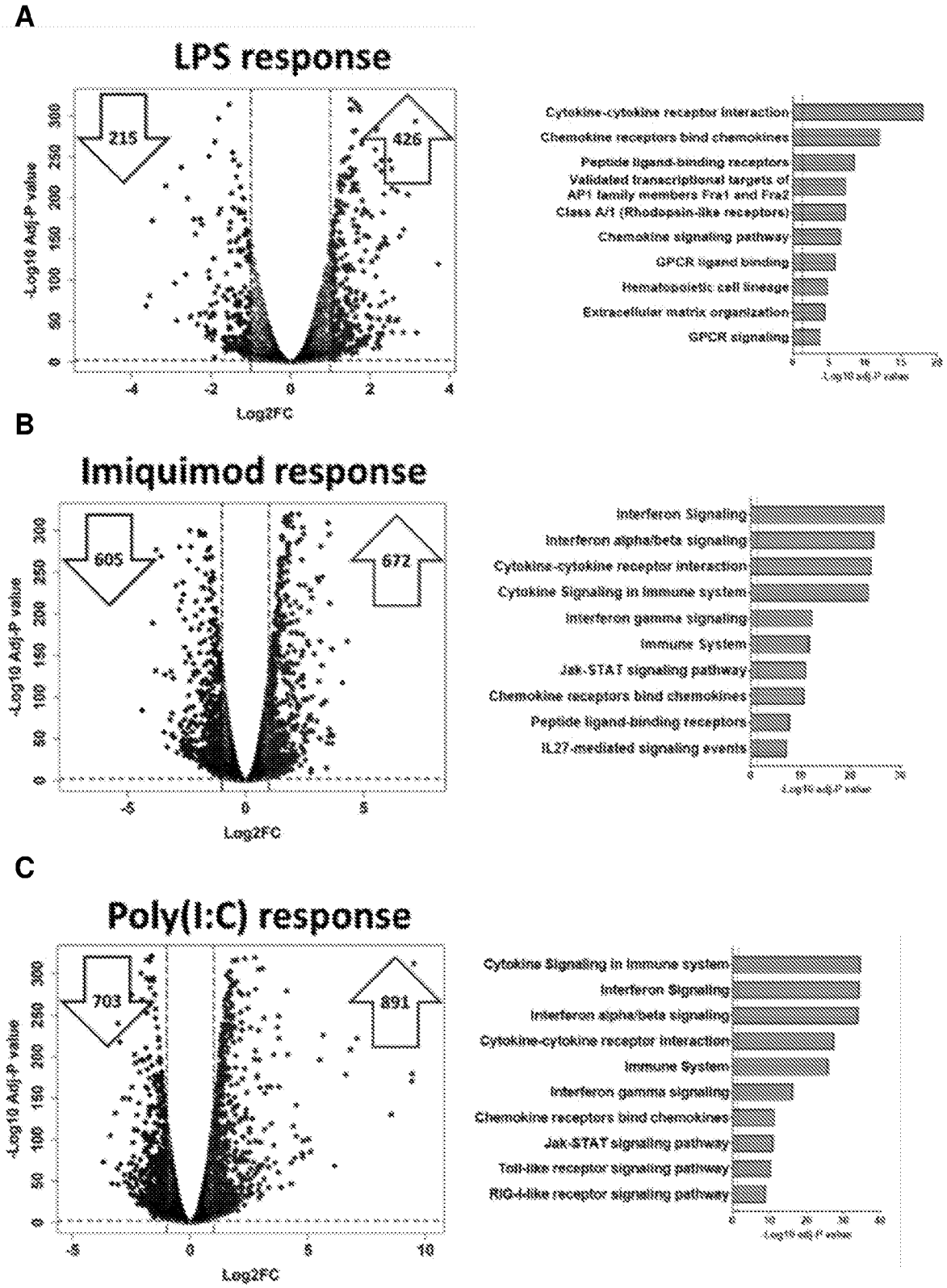
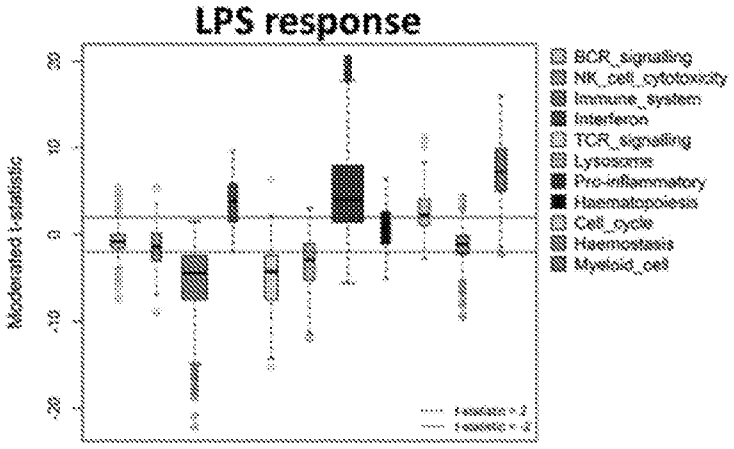
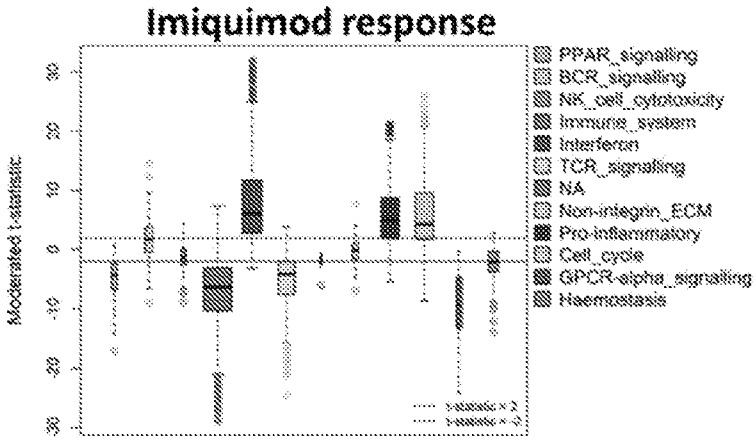

A
LPS response
215
426
-Log10 Adj.P value
Log2FC
Cytokine-cytokine receptor interaction
Chemokine receptors bind chemokines
Peptide ligand-binding receptors
Validated transcriptional targets of AP1 family members Fra1 and Fra2
Class A/1 (Rhodopsin-like receptors)
Chemokine signaling pathway
GPCR ligand binding
Hematopoietic cell lineage
Extracellular matrix organization
GPCR signaling
B
Imiquimod response
605
672
-Log10 Adj.P value
Log2FC
Interferon Signaling
Interferon alpha/beta signaling
Cytokine-cytokine receptor interaction
Cytokine Signaling in Immune system
Interferon gamma signaling
Immune System
Jak-STAT signaling pathway
Chemokine receptors bind chemokines
Peptide ligand-binding receptors
IL27-mediated signaling events
C
Poly(I:C) response
703
891
-Log10 Adj.P value
Log2FC
Cytokine Signaling in Immune system
Interferon Signaling
Interferon alpha/beta signaling
Cytokine-cytokine receptor interaction
Immune System
Interferon gamma signaling
Chemokine receptors bind chemokines
Jak-STAT signaling pathway
Toll-like receptor signaling pathway
RIG-I-like receptor signaling pathway

FIGURE 2 continued

D



E



F

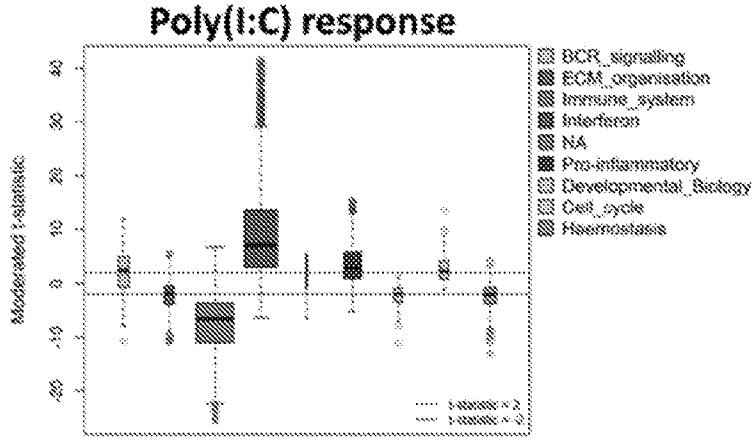
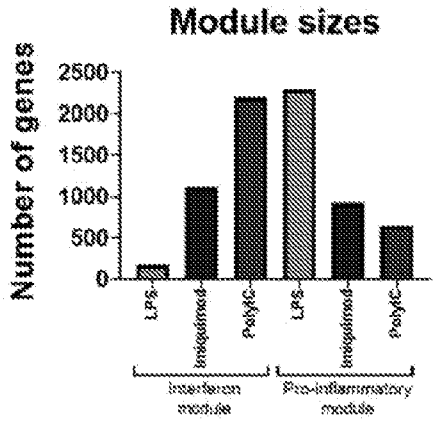


FIGURE 2 continued

G



H

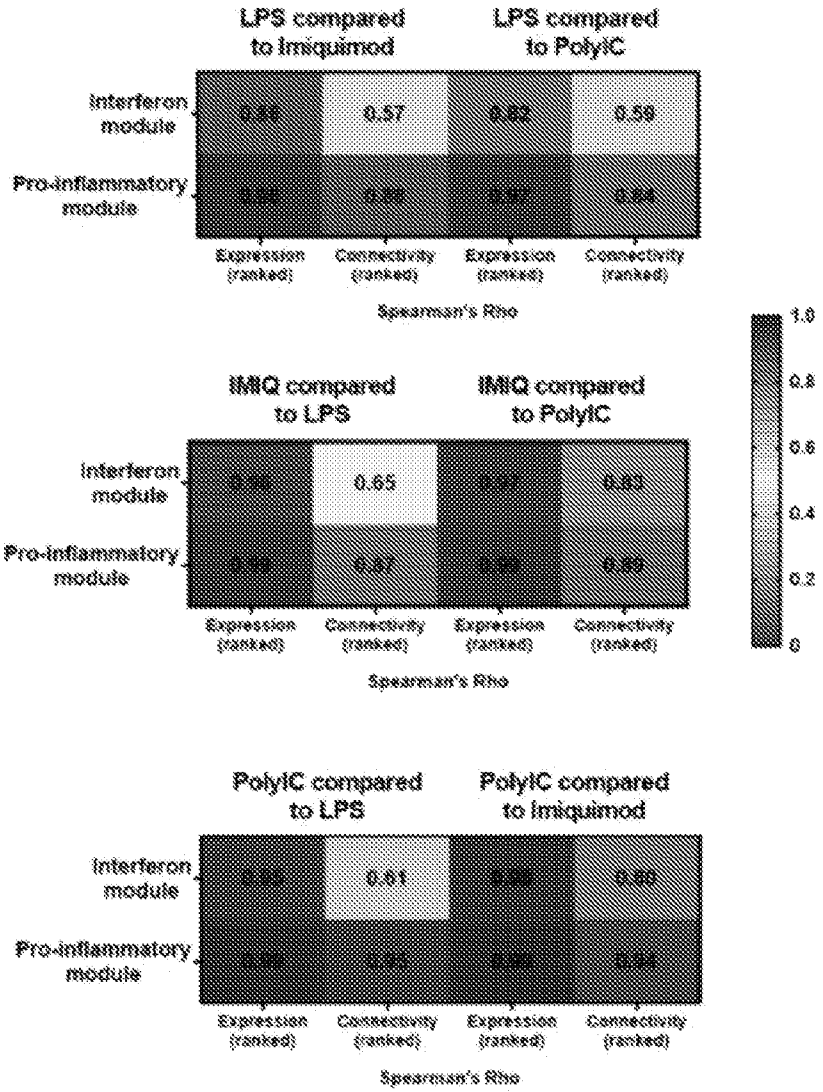


FIGURE 3

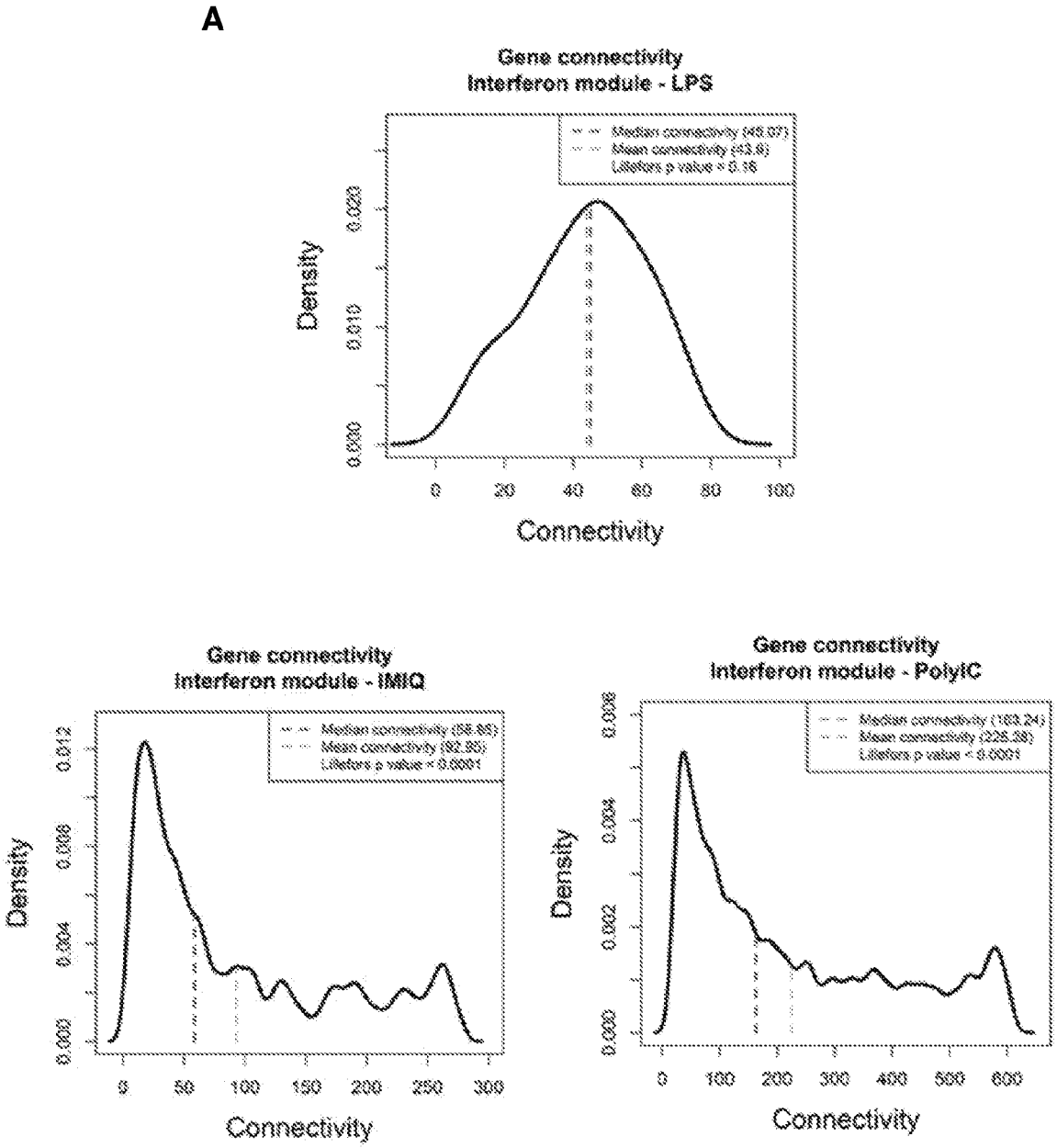
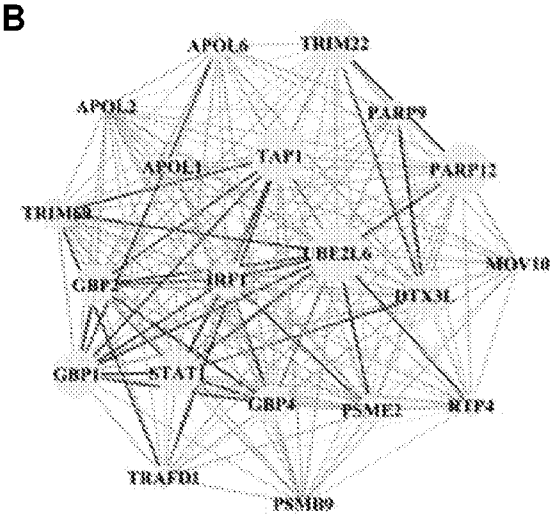
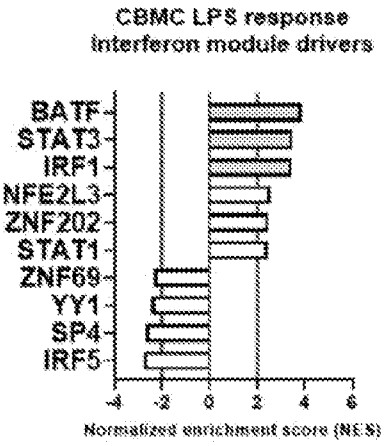

A
Gene connectivity
Interferon module - LPS
Median connectivity (45.07)
Mean connectivity (43.6)
Lilliefors p value = 0.16
Density
0.000
0.010
0.020
0
20
40
60
80
100
Connectivity
Gene connectivity
Interferon module - IMIQ
Median connectivity (58.66)
Mean connectivity (82.35)
Lilliefors p value < 0.0001
Density
0.000
0.004
0.008
0.012
0
50
100
150
200
250
300
Connectivity
Gene connectivity
Interferon module - PolyIC
Median connectivity (163.24)
Mean connectivity (226.38)
Lilliefors p value < 0.0001
Density
0.000
0.002
0.004
0.006
0
100
200
300
400
500
600
Connectivity

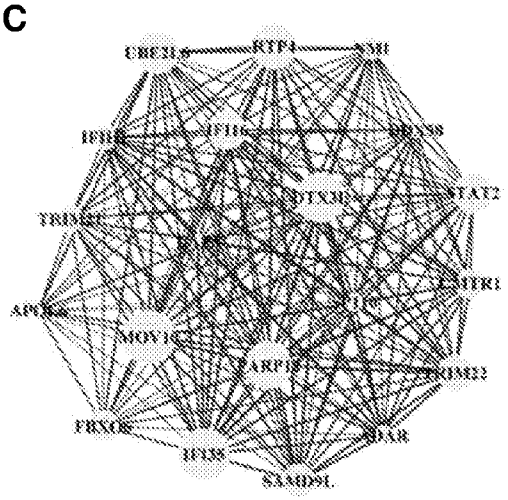
FIGURE 3 continued

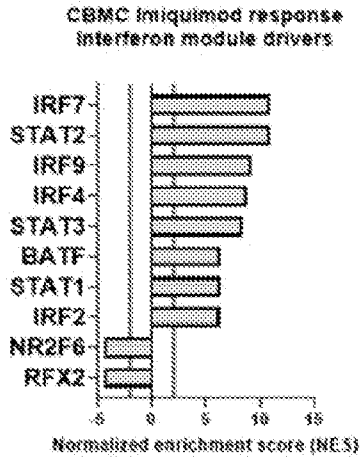
B



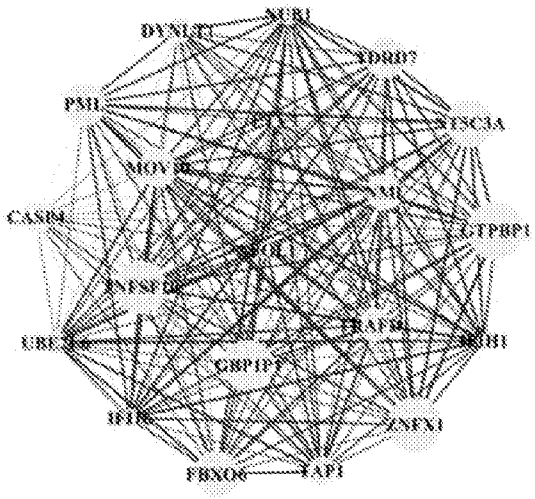


C





D



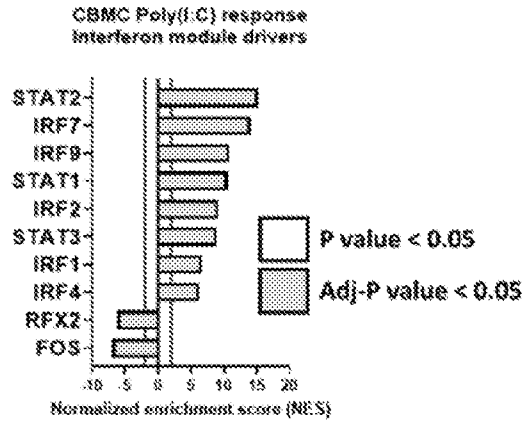


FIGURE 3 continued

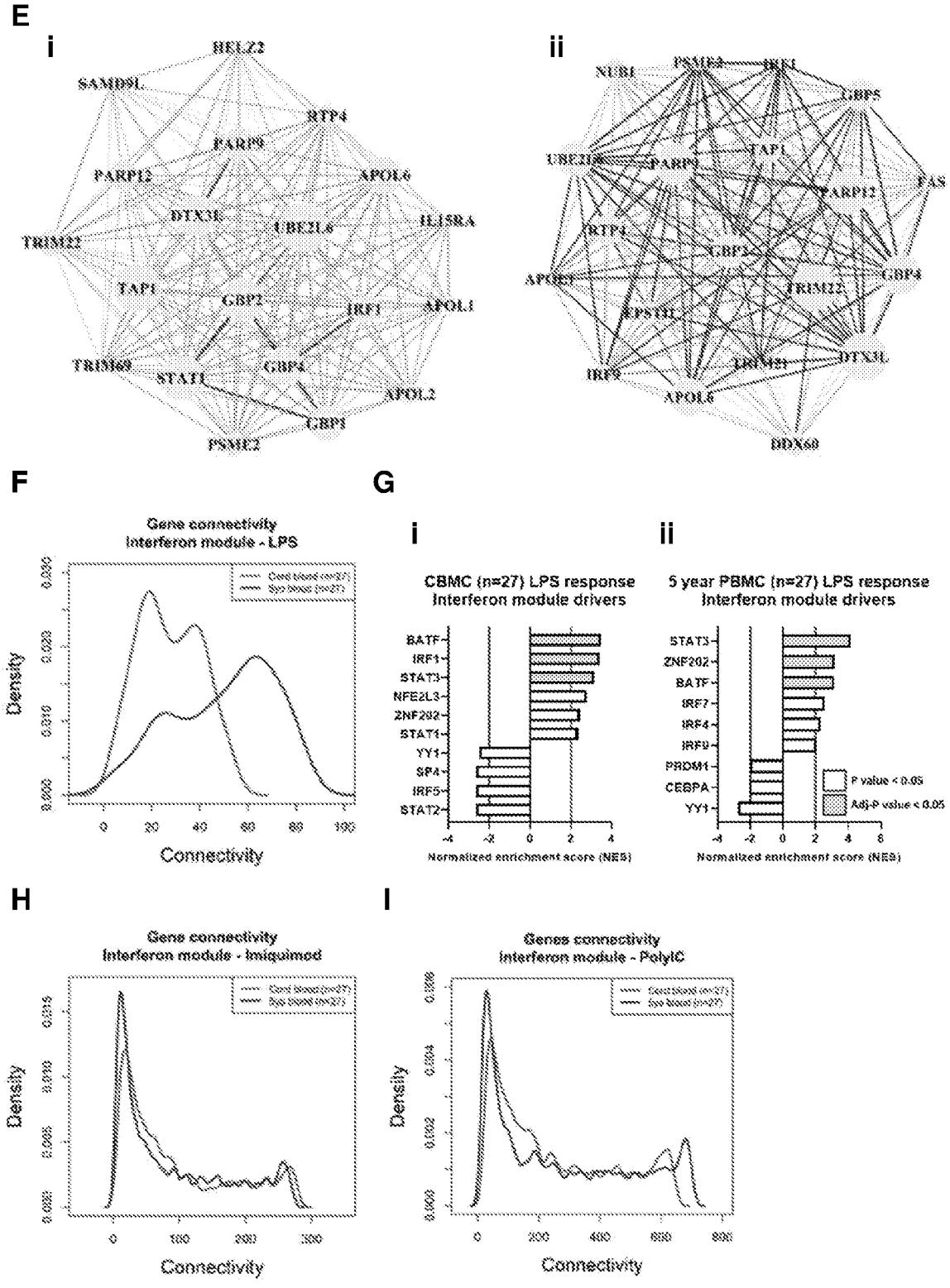
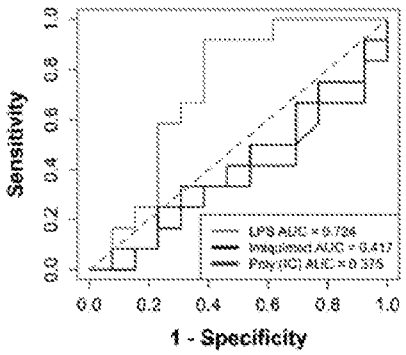
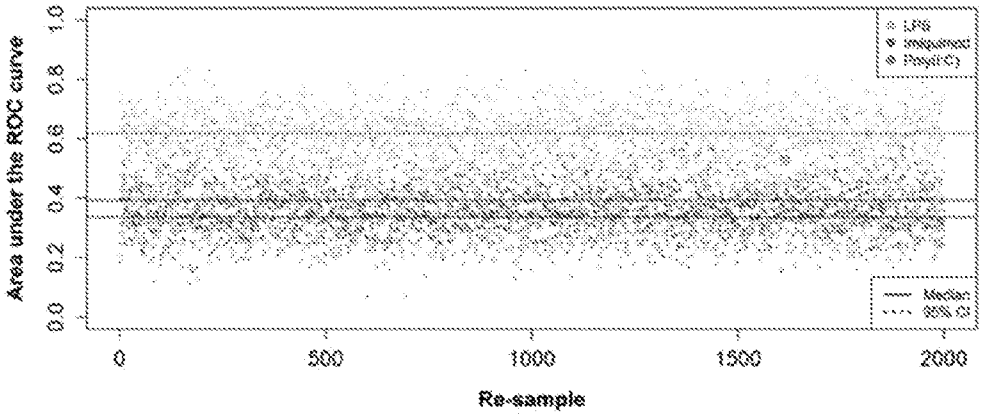


FIGURE 4

A


Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

B


Area under the ROC curve
Re-sample
0
500
1000
1500
2000
0.0
0.2
0.4
0.6
0.8
1.0

FIGUURE 4 continued

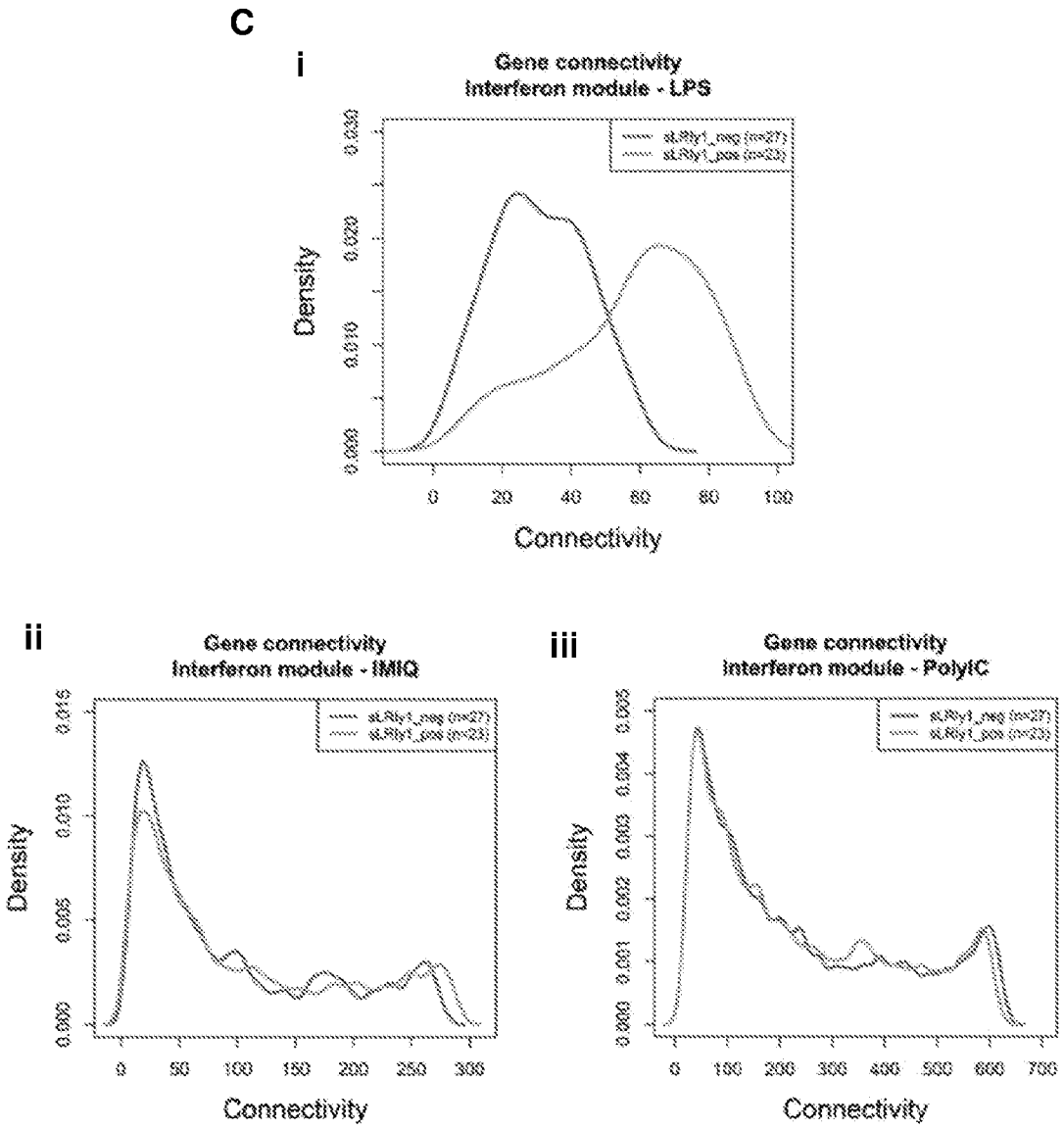
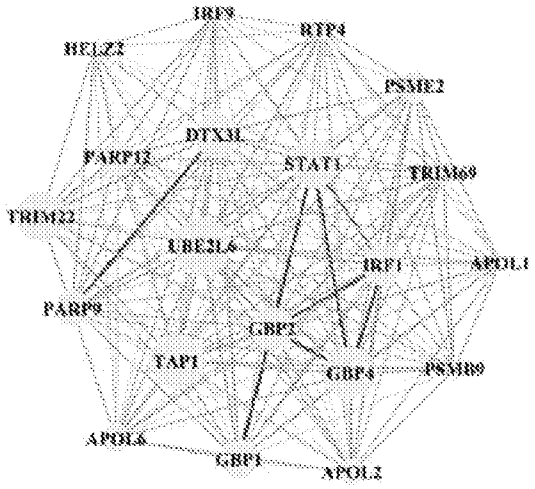


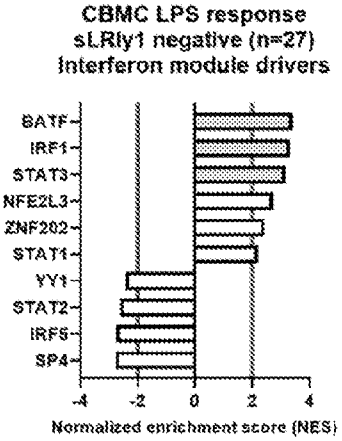
FIGURE 4 continued

D

i

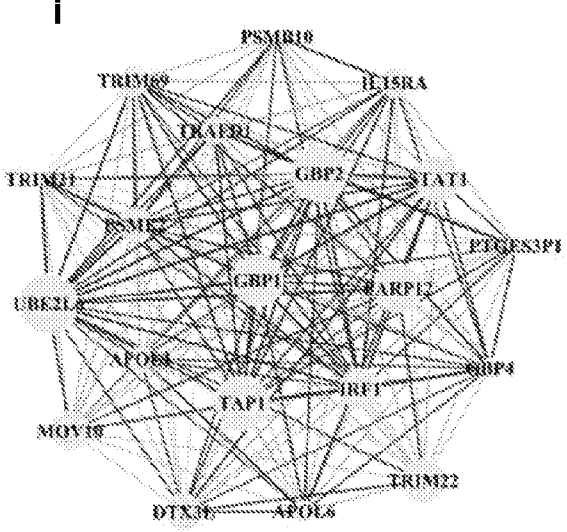


ii



E

i



ii

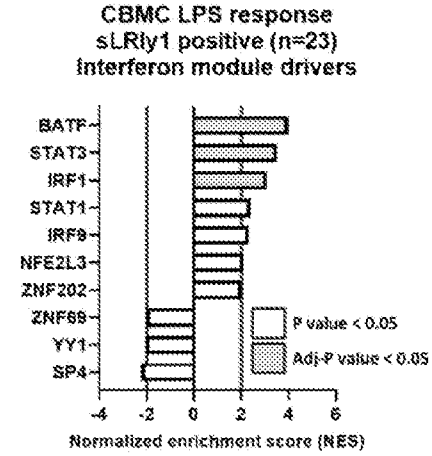
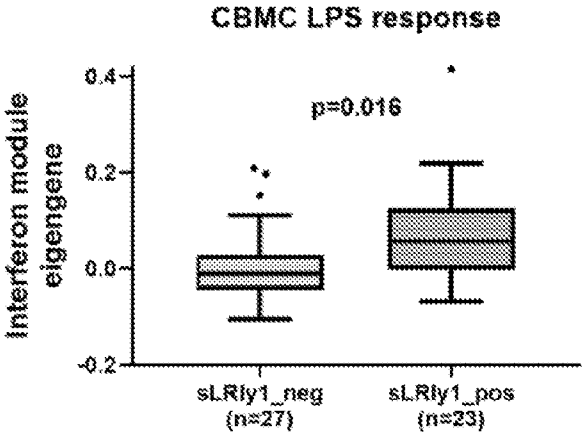


FIGURE 4 continued

F



G

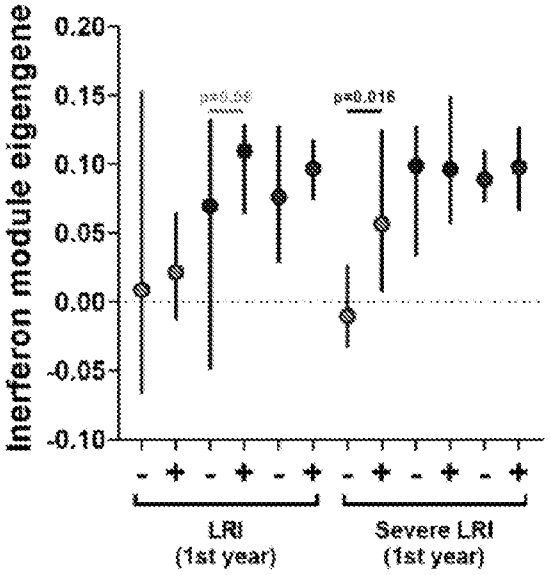


FIGURE 5

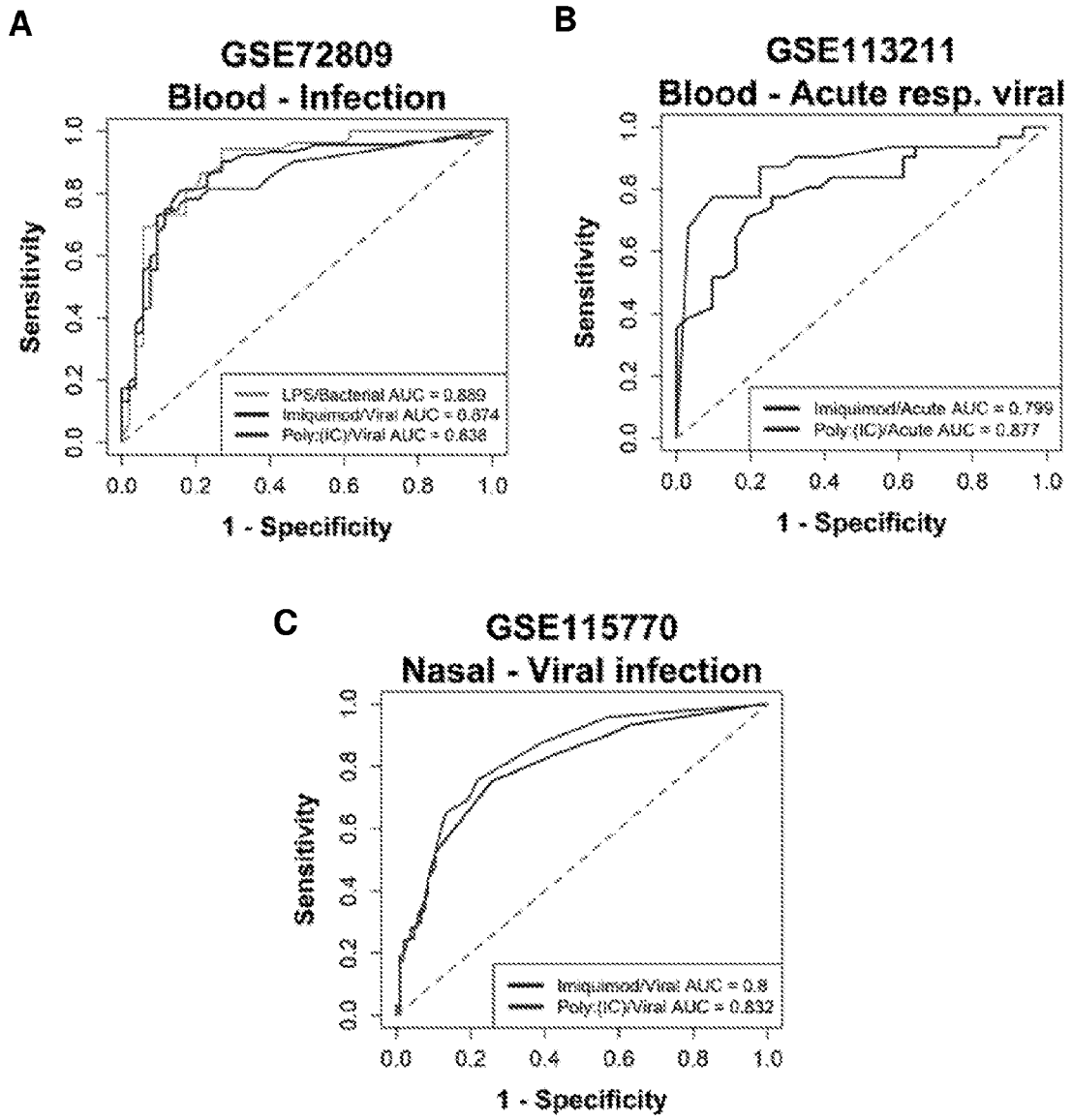

A
GSE72809
Blood - Infection
Sensitivity
1 - Specificity
LPS/Bacterial AUC = 0.889
Imiquimod/Viral AUC = 0.674
Poly(IC)/Viral AUC = 0.638
B
GSE113211
Blood - Acute resp. viral
Sensitivity
1 - Specificity
Imiquimod/Acute AUC = 0.799
Poly(IC)/Acute AUC = 0.877
C
GSE115770
Nasal - Viral infection
Sensitivity
1 - Specificity
Imiquimod/Viral AUC = 0.8
Poly(IC)/Viral AUC = 0.832

FIGURE 5 continued

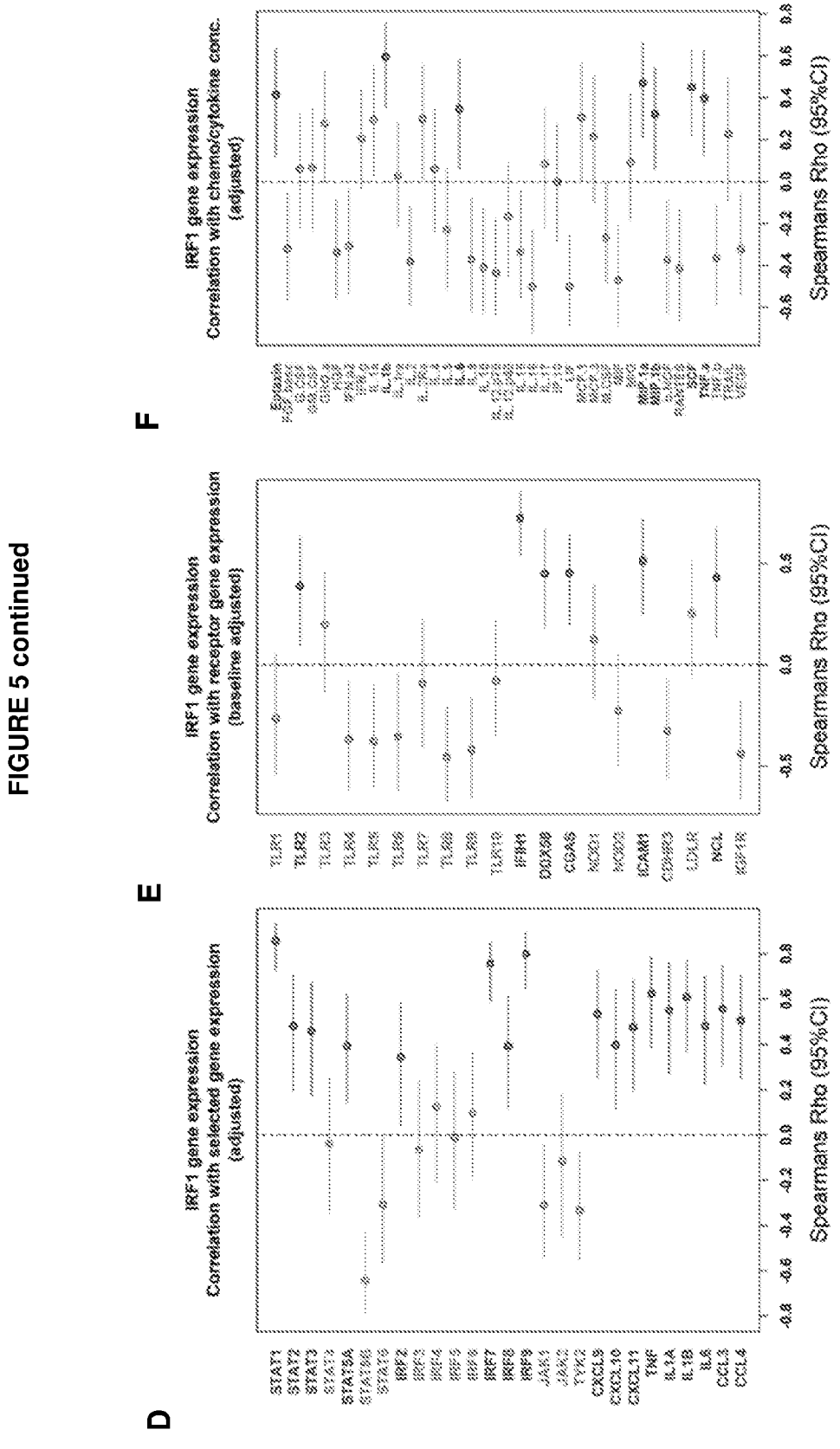
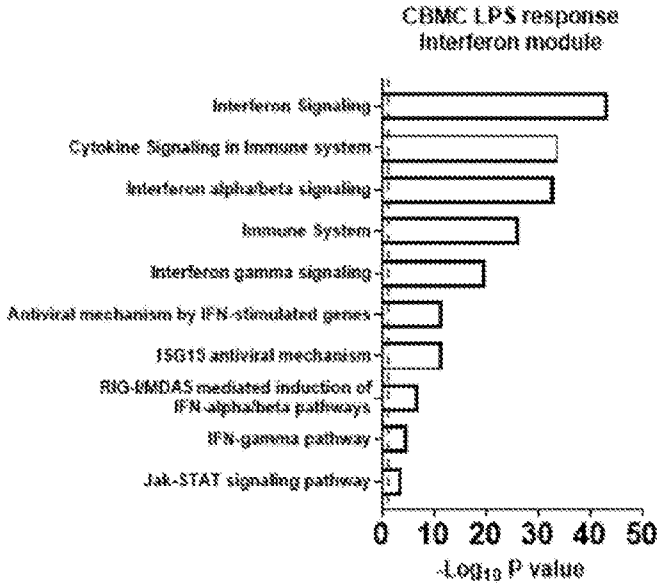


FIGURE 6

A


CBMC LPS response
Interferon module
Interferon Signaling
Cytokine Signaling in Immune system
Interferon alpha/beta signaling
Immune System
Interferon gamma signaling
Antiviral mechanism by IFN-stimulated genes
ISG15 antiviral mechanism
RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways
IFN-gamma pathway
Jak-STAT signaling pathway
0 10 20 30 40 50
-Log10 P value

B

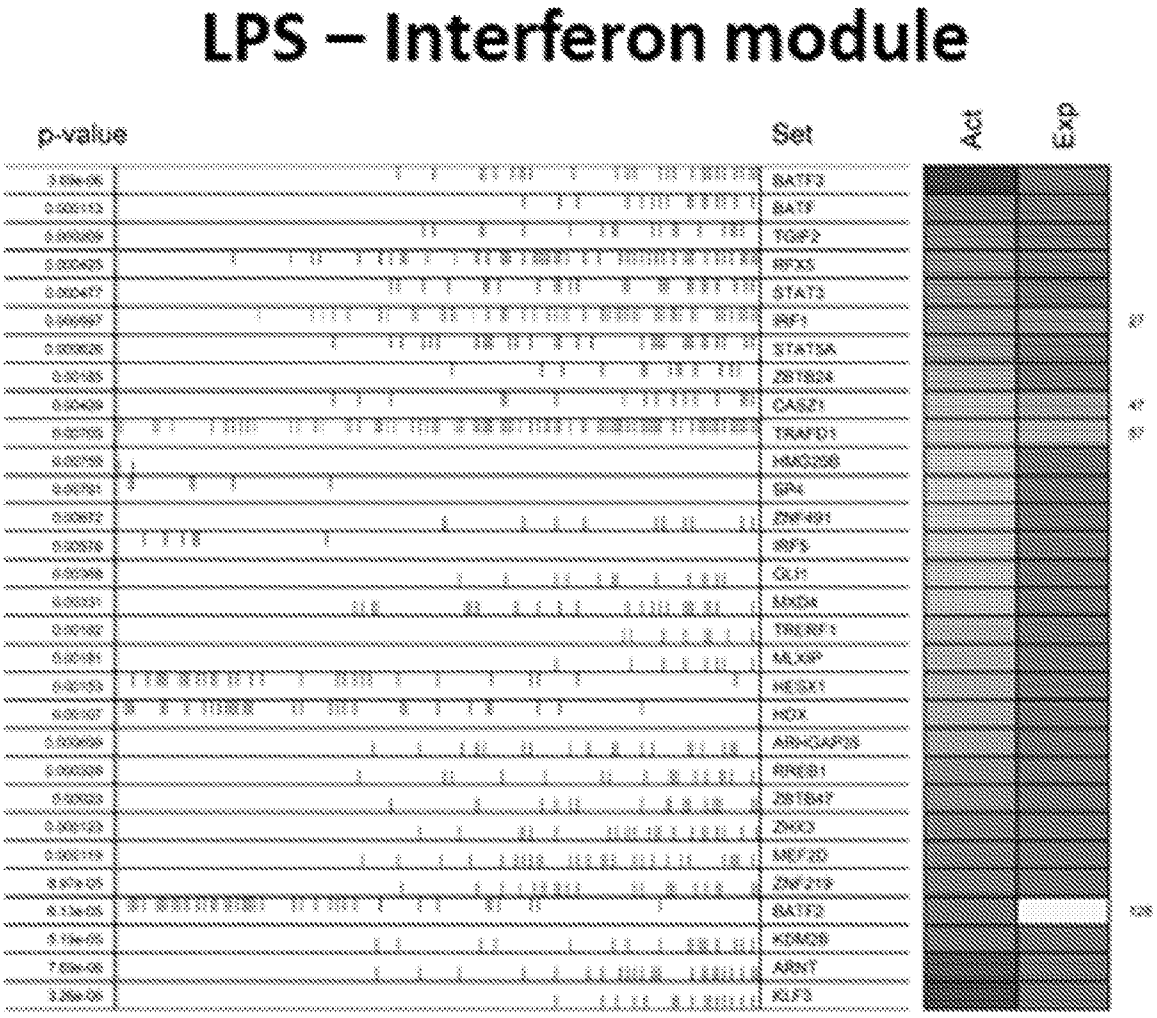

LPS – Interferon module
p-value
Set
Act
Exp

FIGURE 7

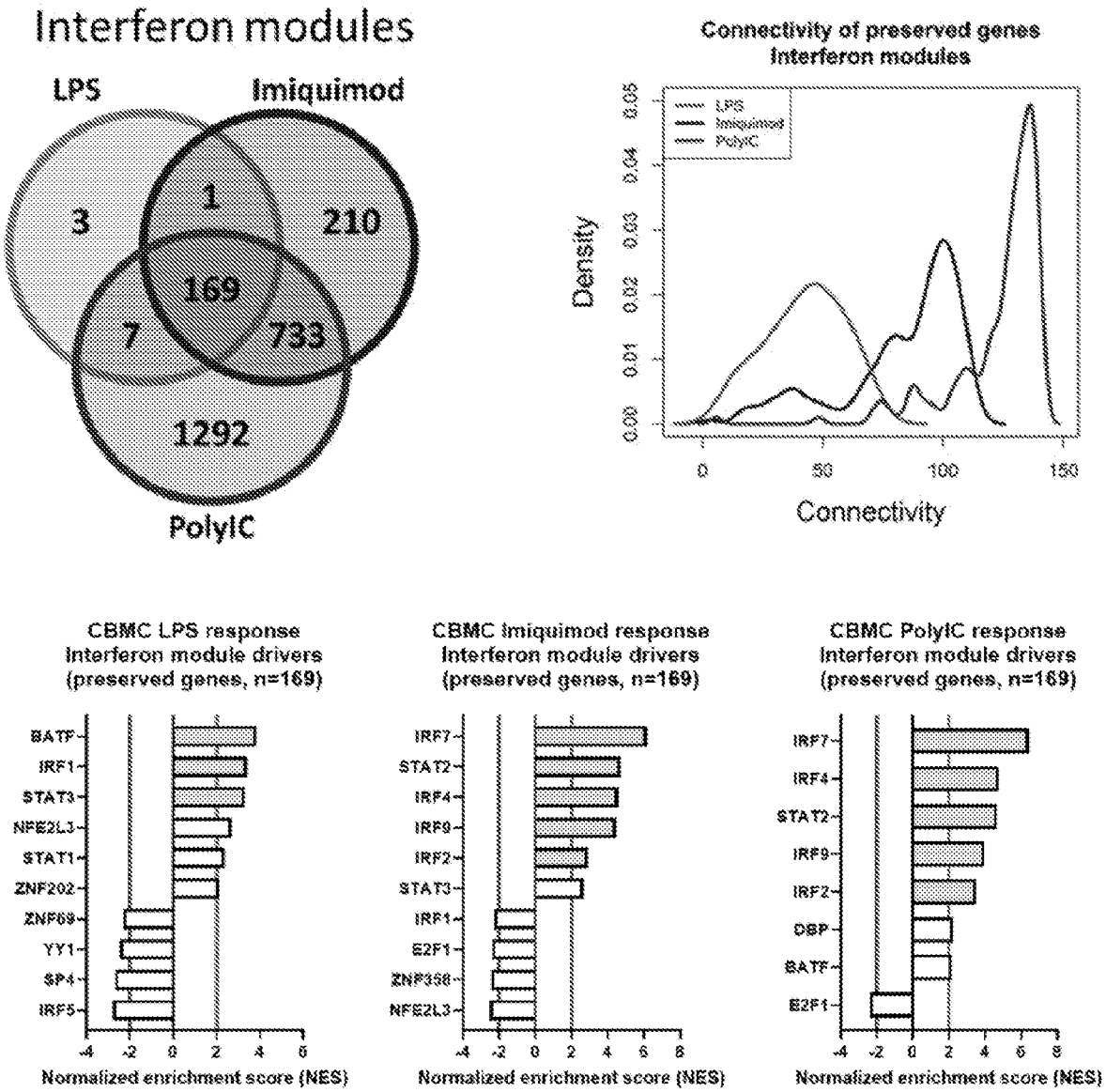

Interferon modules
LPS
Imiquimod
PolyIC
3
1
210
169
7
733
1292
Connectivity of preserved genes
Interferon modules
LPS
Imiquimod
PolyIC
Density
Connectivity
CBMC LPS response
Interferon module drivers
(preserved genes, n=169)
BATF
IRF1
STAT3
NFE2L3
STAT1
ZNF202
ZNF69
YY1
SP4
IRF5
Normalized enrichment score (NES)
CBMC Imiquimod response
Interferon module drivers
(preserved genes, n=169)
IRF7
STAT2
IRF4
IRF9
IRF2
STAT3
IRF1
E2F1
ZNF358
NFE2L3
Normalized enrichment score (NES)
CBMC PolyIC response
Interferon module drivers
(preserved genes, n=169)
IRF7
IRF4
STAT2
IRF9
IRF2
DBP
BATF
E2F1
Normalized enrichment score (NES)

FIGURE 8

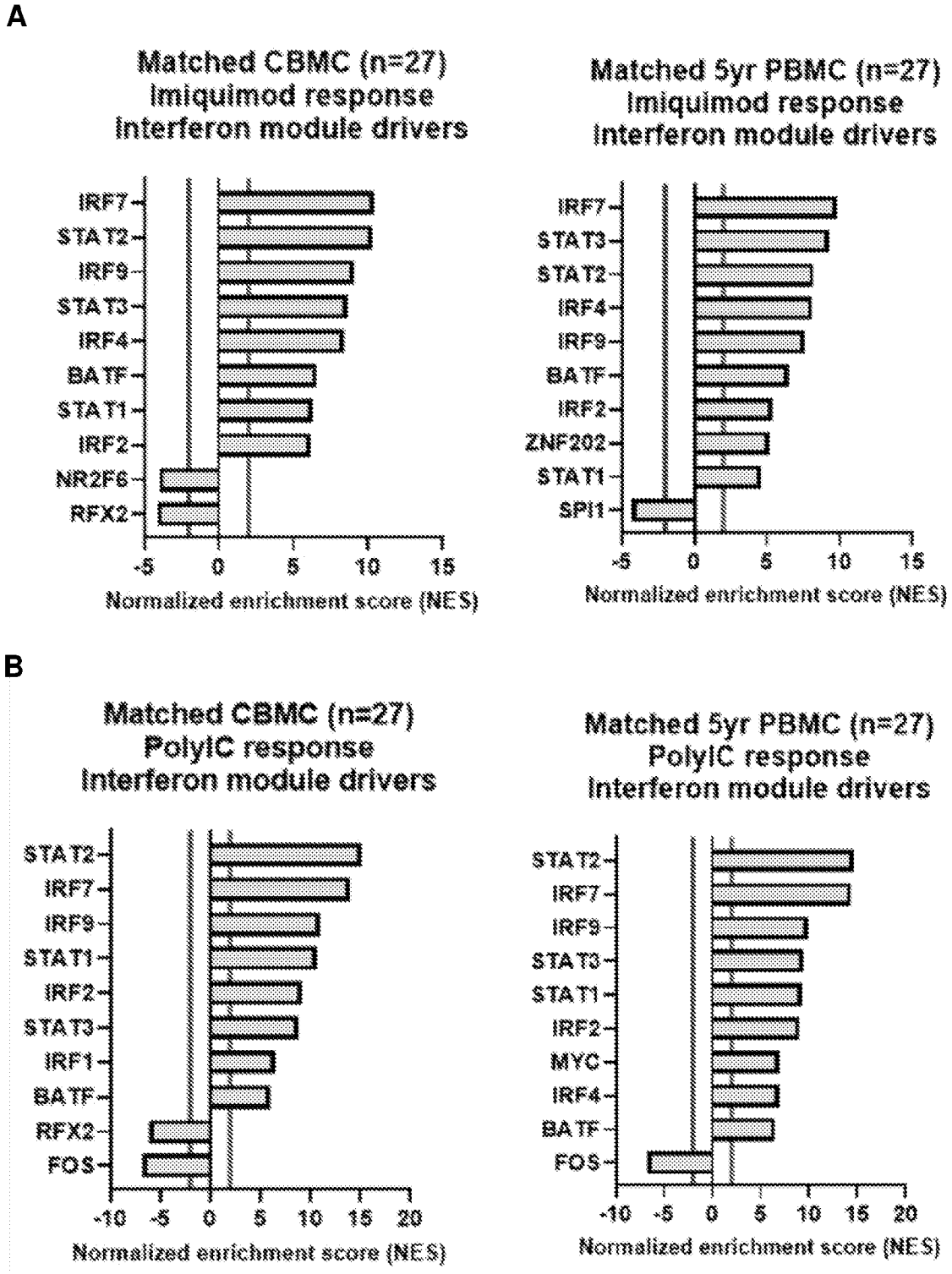

A
Matched CBMC (n=27)
Imiquimod response
Interferon module drivers
IRF7
STAT2
IRF9
STAT3
IRF4
BATF
STAT1
IRF2
NR2F6
RFX2
-5 0 5 10 15
Normalized enrichment score (NES)
Matched 5yr PBMC (n=27)
Imiquimod response
Interferon module drivers
IRF7
STAT3
STAT2
IRF4
IRF9
BATF
IRF2
ZNF202
STAT1
SPI1
-5 0 5 10 15
Normalized enrichment score (NES)
B
Matched CBMC (n=27)
PolyIC response
Interferon module drivers
STAT2
IRF7
IRF9
STAT1
IRF2
STAT3
IRF1
BATF
RFX2
FOS
-10 -5 0 5 10 15 20
Normalized enrichment score (NES)
Matched 5yr PBMC (n=27)
PolyIC response
Interferon module drivers
STAT2
IRF7
IRF9
STAT3
STAT1
IRF2
MYC
IRF4
BATF
FOS
-10 -5 0 5 10 15 20
Normalized enrichment score (NES)

FIGURE 9

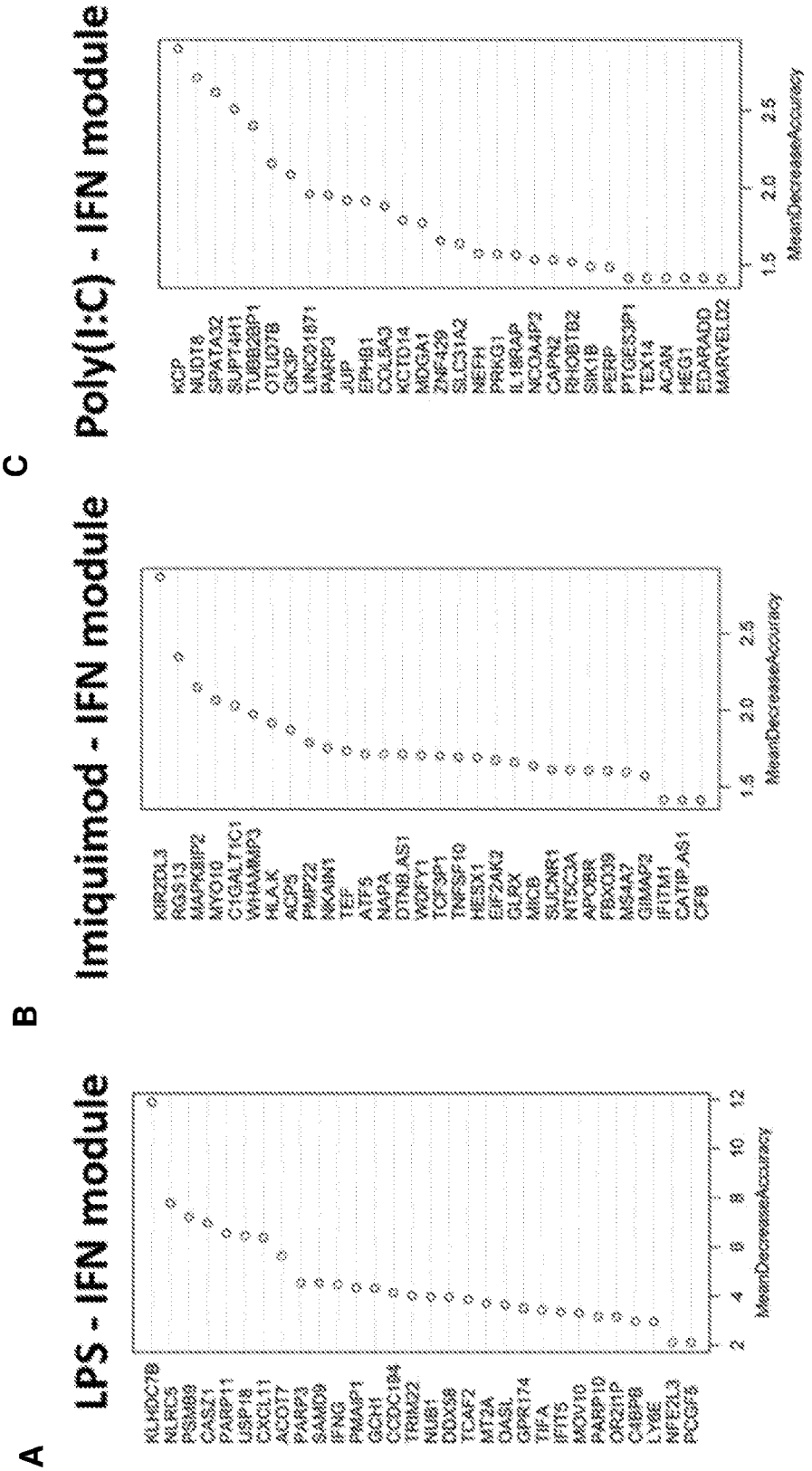

A
LPS - IFN module
KLHDC7B
NLRC5
PSMB8
CASS1
PARP11
USP18
CXCL11
ACOT7
PARP3
SAMD9
IFNG
PMAIP1
GCH1
CCDC104
TRIM22
NUB1
DDX58
TCAF2
MT2A
OASL
GPR174
TIFA
IFIT5
MOV10
PARP10
OR2I1P
C4BPB
LY9E
NFE2L3
PCGF5
MeanDecreaseAccuracy
2
4
6
8
10
12
B
Imiquimod - IFN module
KIR2DL3
RGS13
MAPK8IP2
MYO1G
C1GALT1C1
WHAMMP3
HLA-K
ACP5
PMP22
NKAIN1
TEF
ATF5
MAPA
DTNB-AS1
KMT2E
TCF3P1
TNFSF10
HESX1
EIF2AK3
GLRX
MICB
SLC9A9
MTSCIA
APOBR
FBXO39
MS4A7
GIMAP2
IFITM1
CATIP-AS1
CFB
MeanDecreaseAccuracy
1.5
2.0
2.5
C
Poly(I:C) - IFN module
KCP
MUC16
SPATA32
SUPT4H1
TUBB2BP1
CTU2L7B
GK3P
LINC01871
PARP3
JUP
EPHB1
COL3A3
KCTD14
MOGAT1
ZNF429
SLC31A2
NEFH
PNKD1
IL18RAP
MCOLN2
CAPN2
RHOBTB2
SIK1B
PERP
PTGES3P1
TEX14
ACOT4
HEG1
EDARADD
MARVELD2
MeanDecreaseAccuracy
1.5
2.0
2.5

FIGURE 10

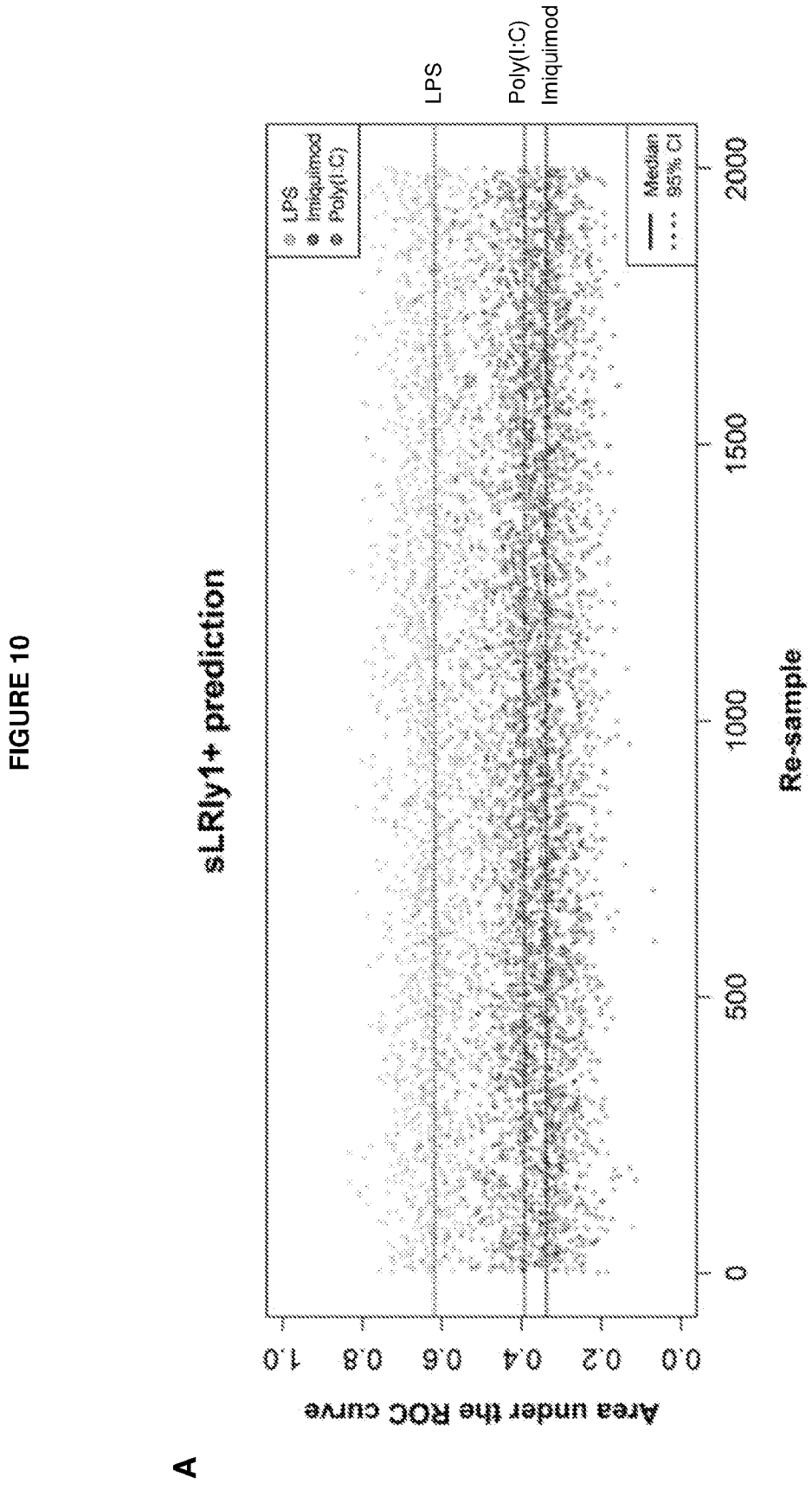

A
sLRly1+ prediction
Area under the ROC curve
0.0
0.2
0.4
0.6
0.8
1.0
Re-sample
0
500
1000
1500
2000
LPS
Poly(I:C)
Imiquimod
LPS
Imiquimod
Poly(I:C)
Median
95% CI

FIGURE 10 continued

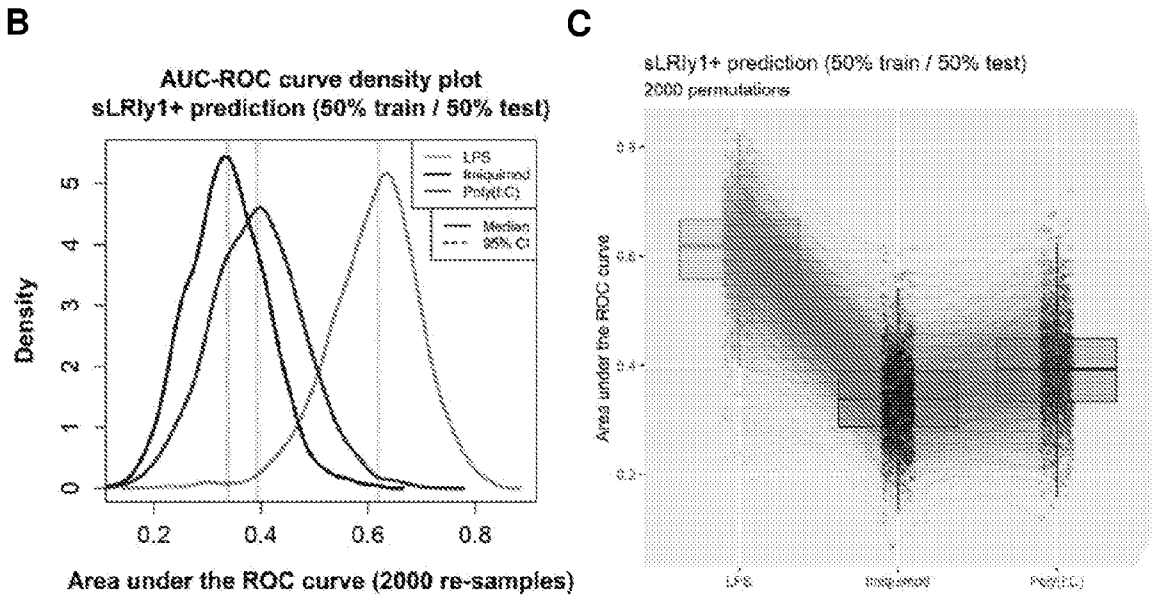


FIGURE 11

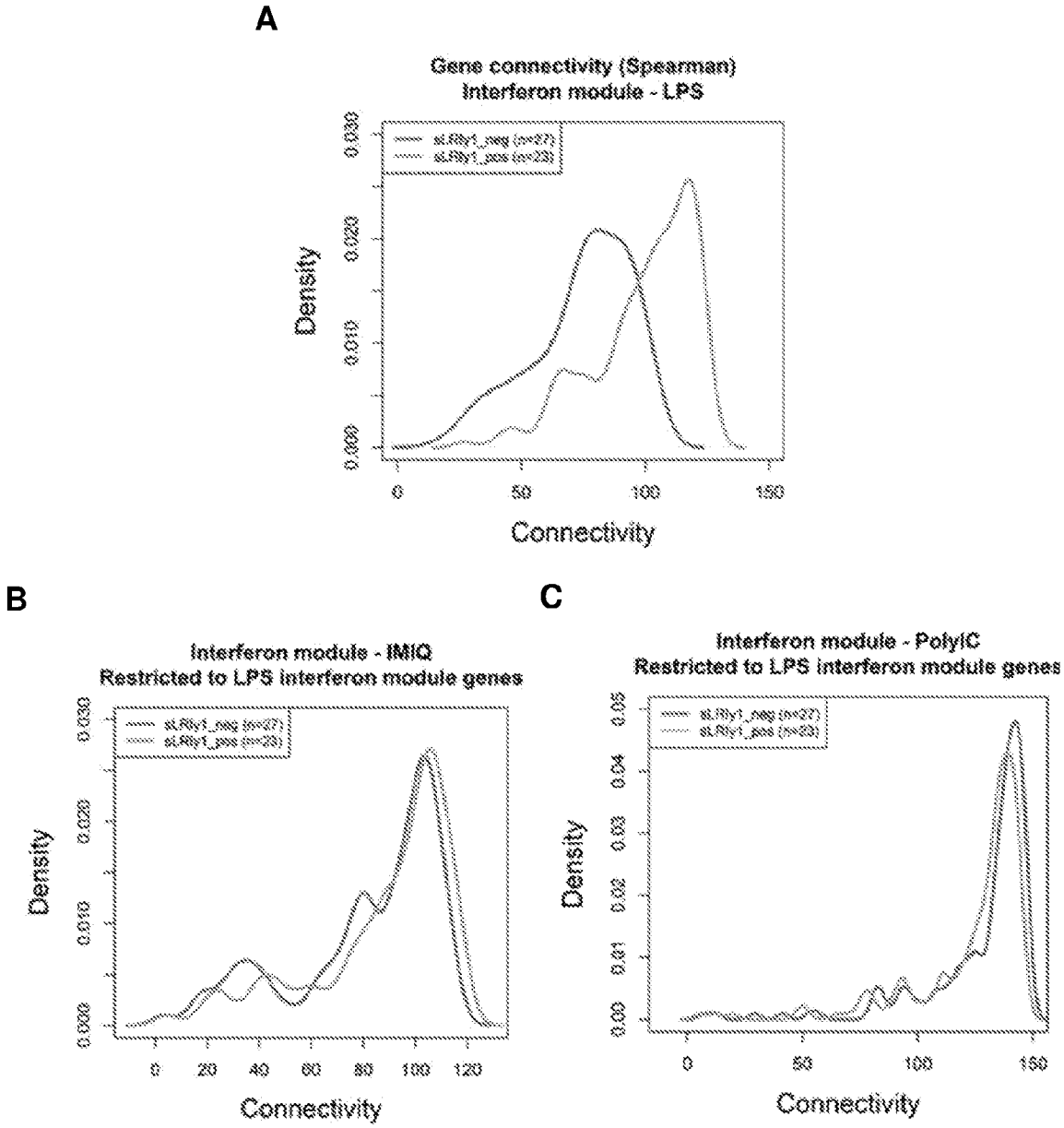
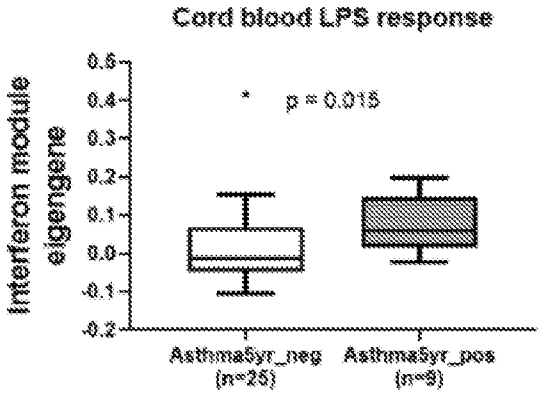

A
Gene connectivity (Spearman)
Interferon module - LPS
Density
Connectivity
B
Interferon module - IMIQ
Restricted to LPS interferon module genes
Density
Connectivity
C
Interferon module - PolyIC
Restricted to LPS interferon module genes
Density
Connectivity

FIGURE 12

A


Cord blood LPS response
Interferon module eigengene
0.6
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
* p = 0.015
Asthma5yr_neg (n=25)
Asthma5yr_pos (n=9)

B

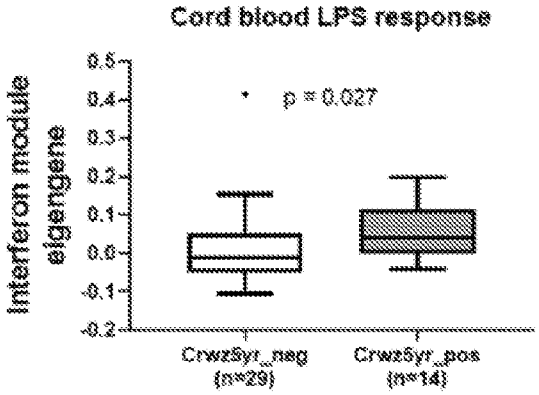

Cord blood LPS response
Interferon module eigengene
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
* p = 0.027
Crwz5yr_neg (n=29)
Crwz5yr_pos (n=14)

FIGURE 13

A

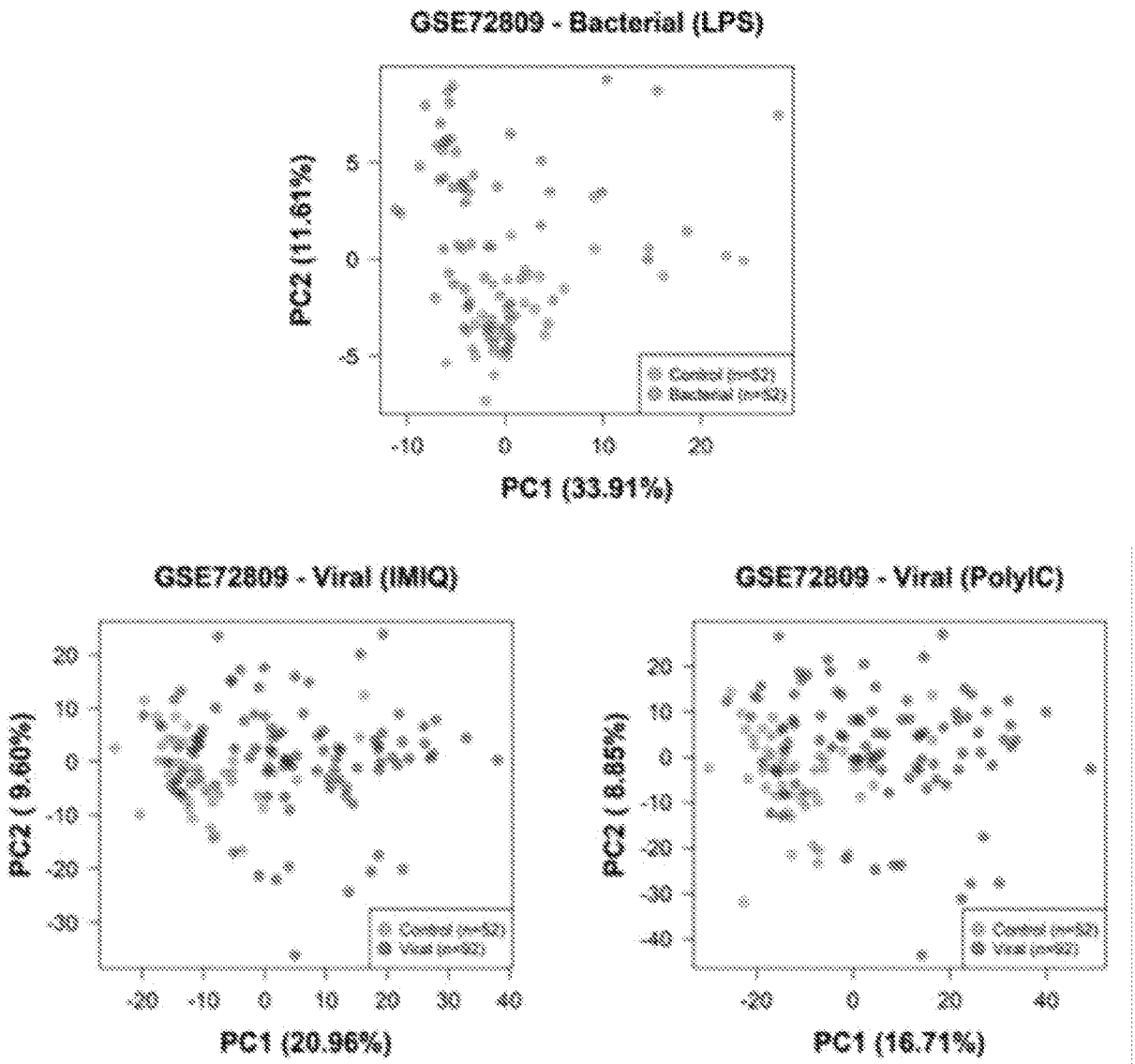
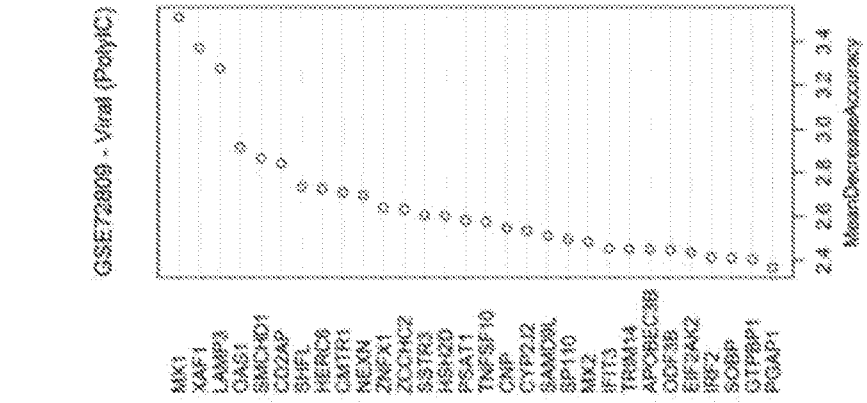
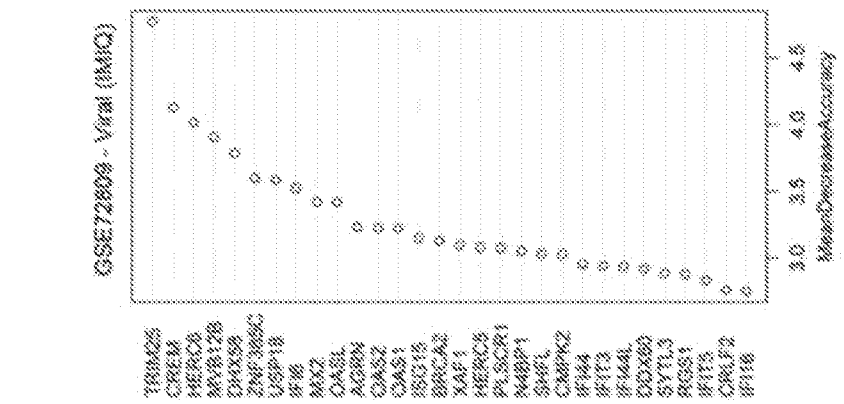

GSE72809 - Bacterial (LPS)
PC2 (11.61%)
PC1 (33.91%)
GSE72809 - Viral (IMIQ)
PC2 (9.60%)
PC1 (20.96%)
GSE72809 - Viral (PolyIC)
PC2 (8.85%)
PC1 (16.71%)

FIGURE 13 continued





B

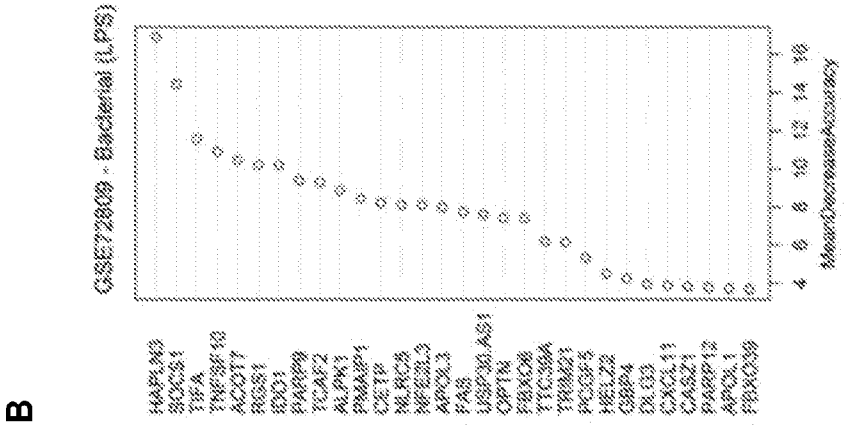


FIGURE 14

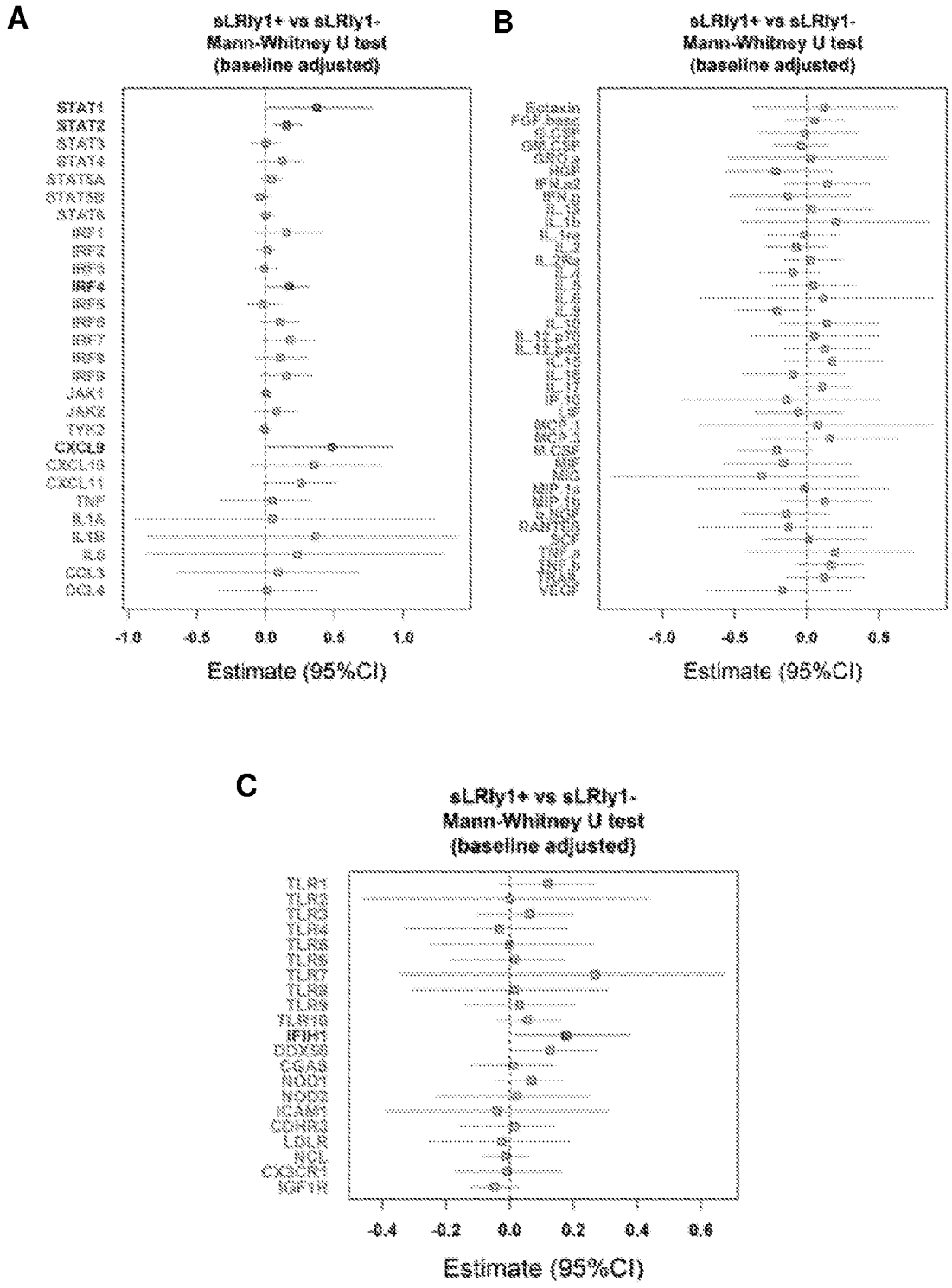
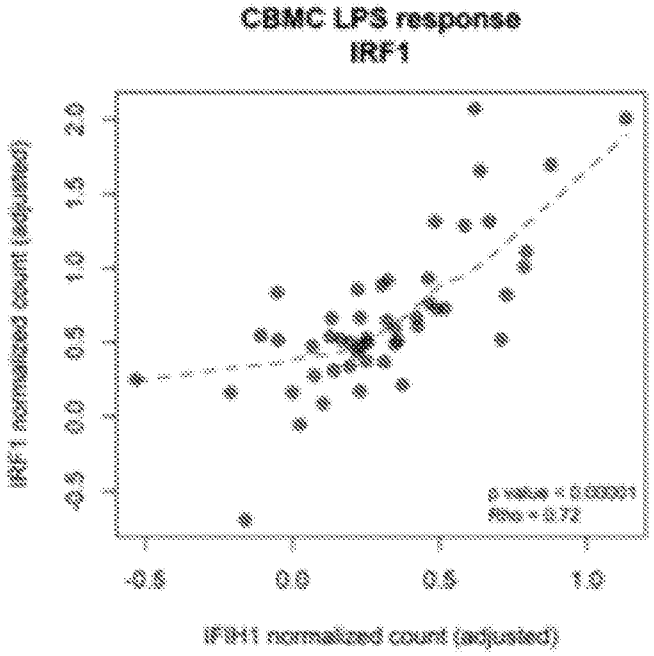

A
sLRIy1+ vs sLRIy1-
Mann-Whitney U test
(baseline adjusted)
STAT1
STAT2
STAT3
STAT4
STAT5A
STAT5B
STAT6
IRF1
IRF2
IRF3
IRF4
IRF5
IRF6
IRF7
IRF8
IRF9
JAK1
JAK2
TYK2
CXCL9
CXCL10
CXCL11
TNF
IL1A
IL1B
IL6
CCL3
CCL4
-1.0
-0.5
0.0
0.5
1.0
Estimate (95%CI)
B
sLRIy1+ vs sLRIy1-
Mann-Whitney U test
(baseline adjusted)
-1.0
-0.5
0.0
0.5
Estimate (95%CI)
C
sLRIy1+ vs sLRIy1-
Mann-Whitney U test
(baseline adjusted)
IRF1
-0.4
-0.2
0.0
0.2
0.4
0.6
Estimate (95%CI)

FIGURE 14 continued

D



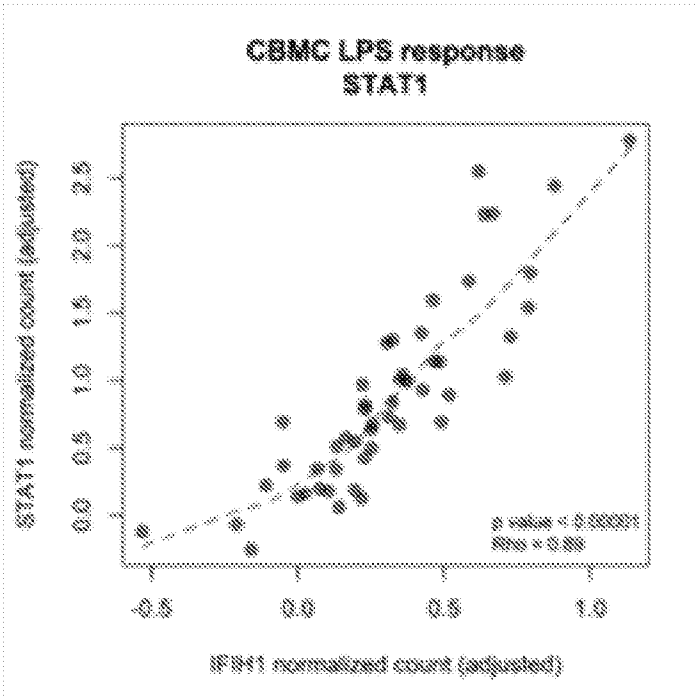


FIGURE 15

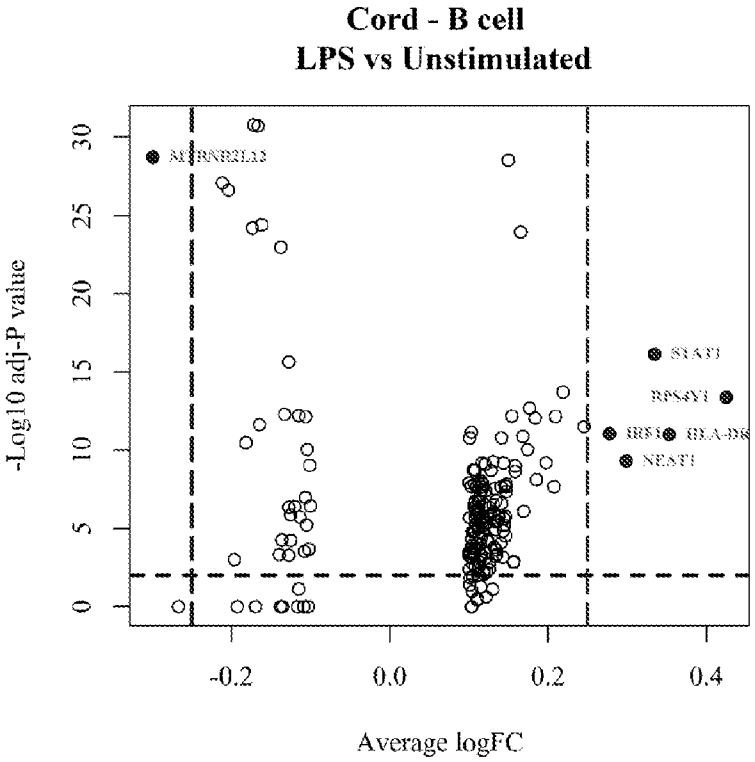

Cord - B cell
LPS vs Unstimulated
-Log10 adj-P value
0
5
10
15
20
25
30
STAT1
IRF1
NFAT1
-0.2
0.0
0.2
0.4
Average logFC

FIGURE 15 continued

