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Figure S1. PRISMA flow-chart of systematic review process for identification of concise transcriptional signatures for the diagnosis of viral infections.

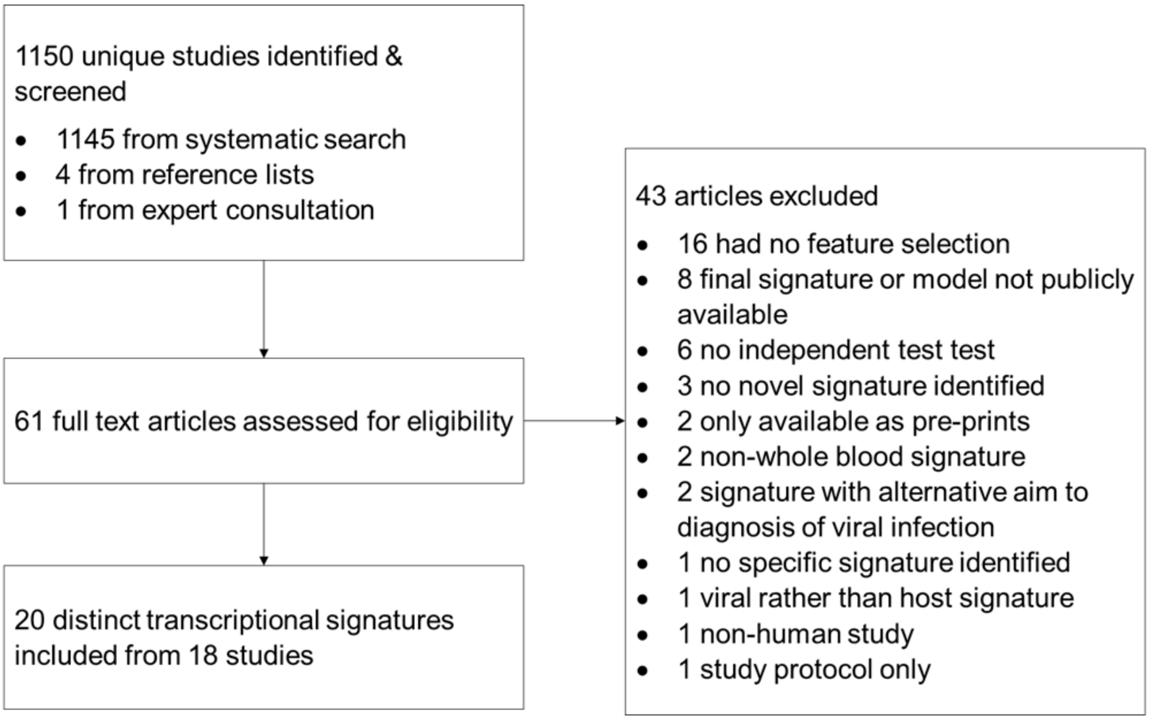
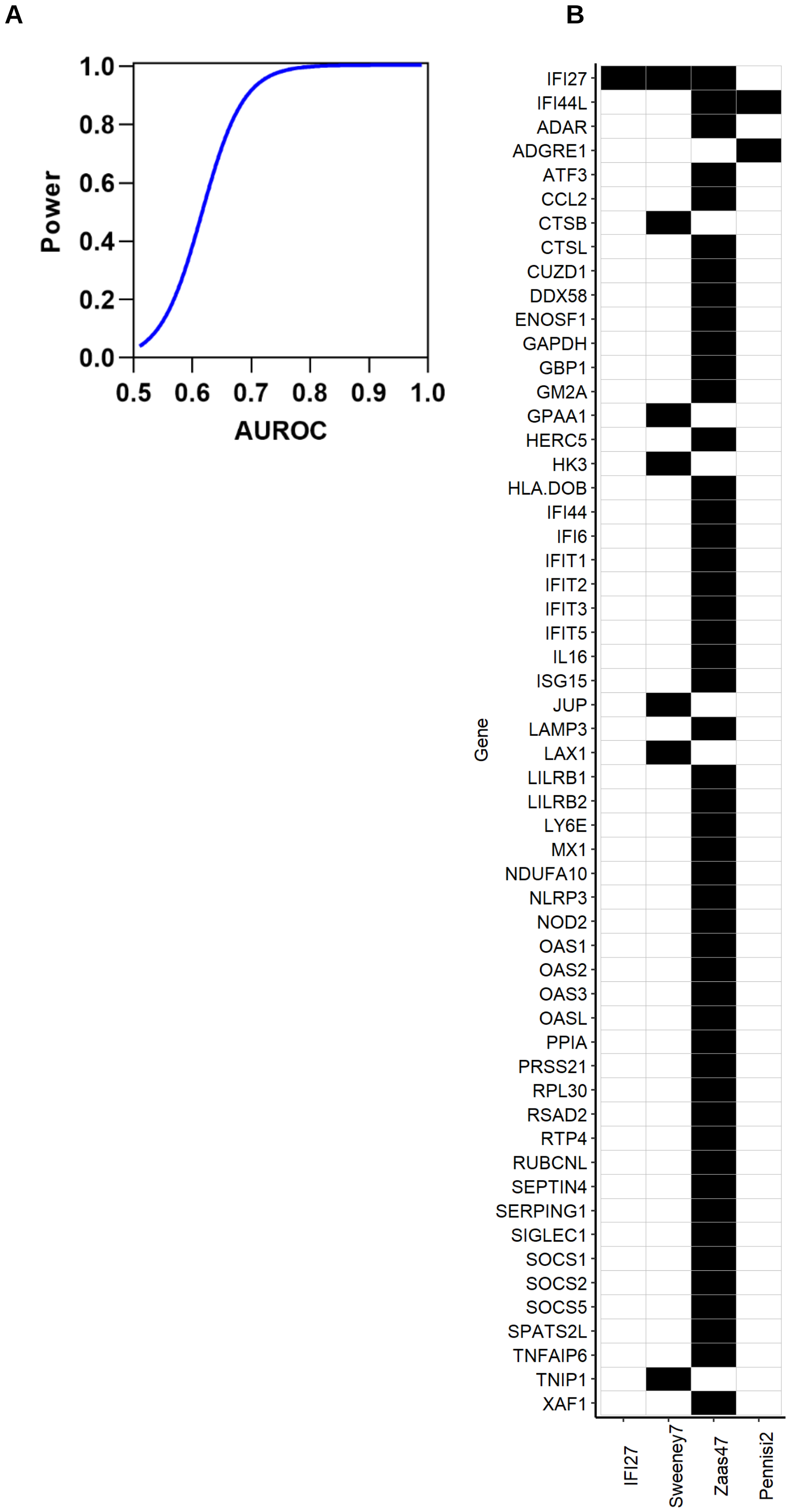


Figure S2. Statistical power and constituent genes comprising four best performing RNA signatures for discriminating participants with contemporaneous PCR-confirmed SARS-CoV-2 infection, compared to uninfected controls.



(A) Statistical power to identify discriminate test-positive cases (N=38) from test-controls (N=55) with a given area under the receiver operating characteristic curve (AUROC) with p-value<0.05 (PASS 2021 Power Analysis and Sample Size Software, version 21.0.2, Utah, USA).

(B) Constituent genes (rows) indicated for each signature (columns). Zaas48 includes 49 gene symbols because 2 genes map to a single microarray probe from the original description.

Figure S3: Peak scores during longitudinal follow-up for best performing RNA signatures to discriminate SARS-CoV-2 cases from heathy controls.

AUC = area under the receiver operating characteristic curve (95% CI).

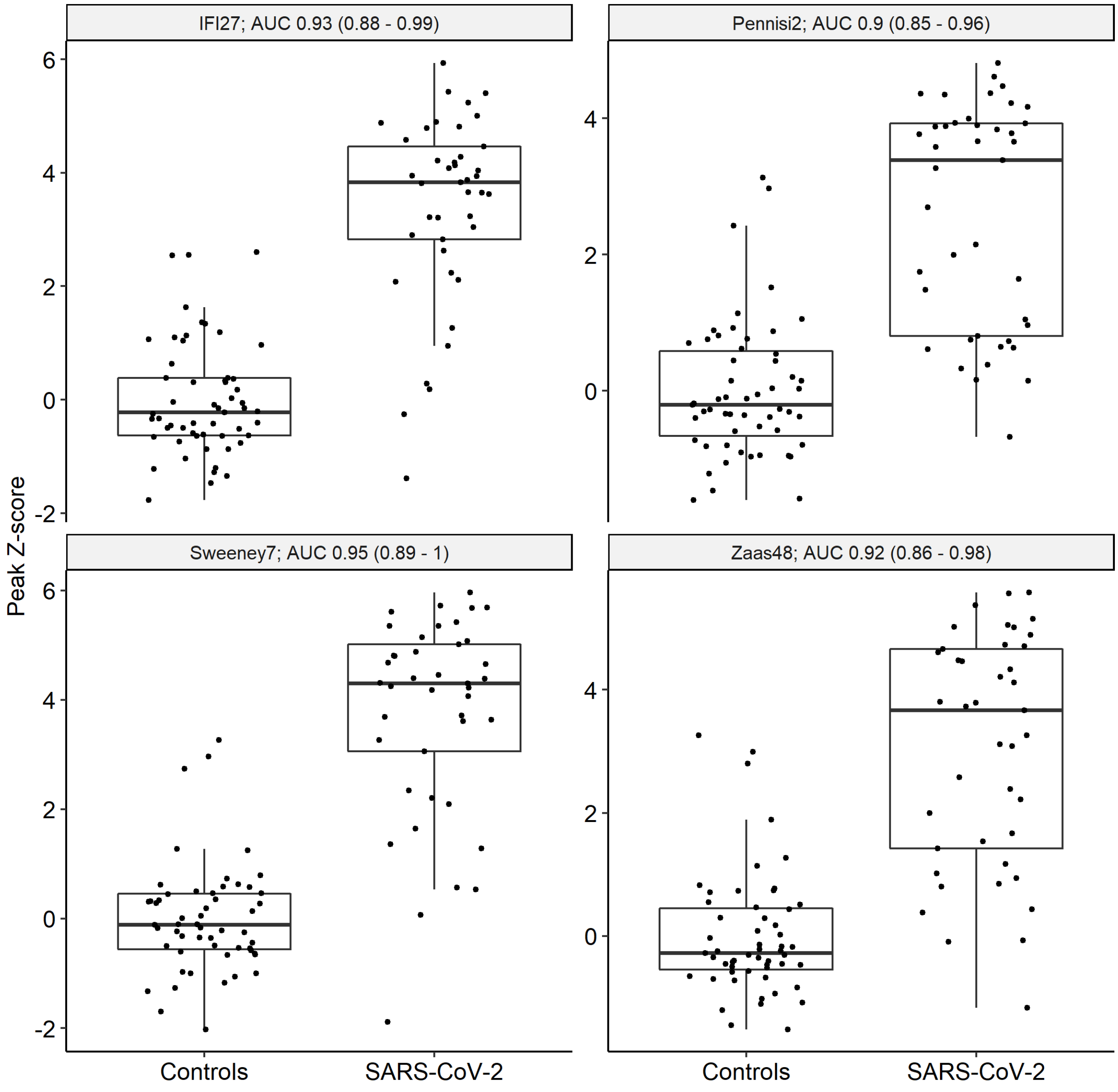


Table S1. Search strategy for systematic Medline search, performed on 12/10/2020.

1. Biomarkers/
2. biomarker*.tw.
3. diagnostic*.tw.
4. signature*.tw.
5. classifier*.tw.
6. 1 or 2 or 3 or 4 or 5
7. Viruses/
8. viral.tw.
9. 7 or 8
10. RNA/
11. Transcriptome/
12. (transcriptom* or transcriptional).tw.
13. (rna or mrna).tw.
14. gene expression.tw.
15. 10 or 11 or 12 or 13 or 14
16. Blood/
17. (host or blood).tw.
18. 16 or 17
19. 6 and 9 and 15 and 18
20. remove duplicates from 19
21. limit 20 to "humans only (removes records about animals)"

Table S2. Baseline characteristics of the study cohort.

Characteristic	**Overall, N = 96**	**Cases, N = 41**[1]	**Controls, N = 55**[1]
Age	36 (27, 47)	36 (28, 46)	36 (26, 50)
Sex			
Female	69 (72%)	28 (68%)	41 (75%)
Male	27 (28%)	13 (32%)	14 (25%)
Ethnicity			
White	66 (69%)	25 (62%)	41 (75%)
Black	6 (6·3%)	5 (12%)	1 (1·8%)
Asian	18 (19%)	9 (22%)	9 (16%)
Other	5 (5·3%)	1 (2·5%)	4 (7·3%)
Unknown	1	1	0
Samples			
1	67 (70%)	12 (29%)	55 (100%)
2	7 (7·3%)	7 (17%)	0 (0%)
3	6 (6·2%)	6 (15%)	0 (0%)
4	10 (10%)	10 (24%)	0 (0%)
5	6 (6·2%)	6 (15%)	0 (0%)
Case-defining symptoms	36 (38%)	31 (76%)	5 (9·1%)

[1] Statistics presented: median (IQR); n (%)

Table S3. Performance metrics of whole-blood RNA signatures whole-blood RNA signatures for discrimination of participants with PCR-confirmed SARS-CoV-2 infection at week prior to first week of PCR-positivity (PCR+ve_-1).

Signature	**AUROC**	**Sensitivity**	**Specificity**
Henrickson16	0·83 (0·71 - 0·96)	0·3 (0·11 - 0·6)	0·93 (0·83 - 0·97)
IFIT3	0·82 (0·69 - 0·94)	0·3 (0·11 - 0·6)	0·93 (0·83 - 0·97)
AndresTerre11	0·82 (0·65 - 0·99)	0·3 (0·11 - 0·6)	0·95 (0·85 - 0·98)
Pennisi2	0·8 (0·64 - 0·95)	0·3 (0·11 - 0·6)	0·95 (0·85 - 0·98)
Zaas48	0·78 (0·6 - 0·97)	0·4 (0·17 - 0·69)	0·95 (0·85 - 0·98)
TrouilletAssant6	0·78 (0·6 - 0·96)	0·3 (0·11 - 0·6)	0·93 (0·83 - 0·97)
IFI27	0·78 (0·59 - 0·97)	0·4 (0·17 - 0·69)	0·95 (0·85 - 0·98)
IFI44L	0·77 (0·6 - 0·95)	0·3 (0·11 - 0·6)	0·95 (0·85 - 0·98)
RSAD2	0·77 (0·6 - 0·95)	0·3 (0·11 - 0·6)	0·93 (0·83 - 0·97)
Sampson4	0·75 (0·58 - 0·93)	0·3 (0·11 - 0·6)	0·93 (0·83 - 0·97)
Sweeney7	0·75 (0·52 - 0·98)	0·4 (0·17 - 0·69)	0·95 (0·85 - 0·98)
Herberg2	0·73 (0·54 - 0·92)	0·3 (0·11 - 0·6)	0·93 (0·83 - 0·97)
Lydon15	0·7 (0·49 - 0·91)	0·3 (0·11 - 0·6)	0·95 (0·85 - 0·98)
Tsalik33	0·68 (0·5 - 0·86)	0·2 (0·06 - 0·51)	0·98 (0·9 - 1)
MX1	0·67 (0·43 - 0·92)	0·3 (0·11 - 0·6)	0·95 (0·85 - 0·98)
Yu3	0·63 (0·44 - 0·83)	0 (0 - 0·28)	1 (0·93 - 1)
Lopez7	0·62 (0·39 - 0·85)	0·2 (0·06 - 0·51)	0·98 (0·9 - 1)
Sampson10	0·57 (0·32 - 0·83)	0·3 (0·11 - 0·6)	0·95 (0·85 - 0·98)
OLFM4	0·49 (0·29 - 0·69)	1 (0·72 - 1)	0·02 (0 - 0·1)
Sweeney11	0·49 (0·26 - 0·72)	0·9 (0·6 - 0·99)	0·04 (0·01 - 0·12)

Includes 10 subsequently SARS-CoV-2 positive participants and 55 uninfected controls. Discrimination is shown as area under the receiver operating characteristic curve (AUROC). Sensitivity and specificity are shown using pre-defined thresholds of 2 standard deviations above the mean of the uninfected control population (Z2). All metrics as shown as point estimates (95% confidence intervals).

Table S4. Performance metrics of whole-blood RNA signatures for discrimination of participants with PCR-confirmed SARS-CoV-2 infection at week of first week of PCR-positivity (PCR+ve_0) from uninfected controls, excluding participants with contemporaneous symptoms at the time of nasopharyngeal swab sampling.

Signature	AUROC	Sensitivity	Specificity
IFI27	0·96 (0·92 - 1)	0·86 (0·69 - 0·95)	0·95 (0·85 - 0·98)
Sweeney7	0·95 (0·9 - 1)	0·86 (0·69 - 0·95)	0·95 (0·85 - 0·98)
Zaas48	0·94 (0·89 - 0·99)	0·62 (0·44 - 0·77)	0·95 (0·85 - 0·98)
Pennisi2	0·92 (0·86 - 0·97)	0·62 (0·44 - 0·77)	0·95 (0·85 - 0·98)
IFI44L	0·91 (0·85 - 0·97)	0·55 (0·38 - 0·72)	0·95 (0·85 - 0·98)
AndresTerre11	0·9 (0·83 - 0·96)	0·55 (0·38 - 0·72)	0·95 (0·85 - 0·98)
Henrickson16	0·89 (0·82 - 0·97)	0·55 (0·38 - 0·72)	0·93 (0·83 - 0·97)
Lydon15	0·88 (0·81 - 0·96)	0·59 (0·41 - 0·74)	0·95 (0·85 - 0·98)
TrouilletAssant6	0·88 (0·8 - 0·95)	0·52 (0·34 - 0·69)	0·93 (0·83 - 0·97)
Herberg2	0·85 (0·77 - 0·94)	0·48 (0·31 - 0·66)	0·93 (0·83 - 0·97)
RSAD2	0·84 (0·75 - 0·93)	0·48 (0·31 - 0·66)	0·93 (0·83 - 0·97)
Sampson4	0·84 (0·75 - 0·93)	0·52 (0·34 - 0·69)	0·93 (0·83 - 0·97)
MX1	0·83 (0·73 - 0·92)	0·45 (0·28 - 0·62)	0·95 (0·85 - 0·98)
Sampson10	0·82 (0·72 - 0·92)	0·52 (0·34 - 0·69)	0·95 (0·85 - 0·98)
Tsalik33	0·8 (0·7 - 0·9)	0·41 (0·26 - 0·59)	0·98 (0·9 - 1)
Lopez7	0·79 (0·69 - 0·9)	0·38 (0·23 - 0·56)	0·98 (0·9 - 1)
IFIT3	0·76 (0·64 - 0·88)	0·45 (0·28 - 0·62)	0·93 (0·83 - 0·97)
OLFM4	0·6 (0·47 - 0·73)	0 (0 - 0·12)	0·98 (0·9 - 1)
Sweeney11	0·57 (0·43 - 0·71)	0·1 (0·04 - 0·26)	0·96 (0·88 - 0·99)
Yu3	0·57 (0·43 - 0·71)	0·07 (0·02 - 0·22)	1 (0·93 - 1)

Includes 29 contemporaneous SARS-CoV-2 positive samples and 55 uninfected controls. Discrimination is shown as area under the receiver operating characteristic curve (AUROC). Sensitivity and specificity are shown using pre-defined thresholds of 2 standard deviations above the mean of the uninfected control population (Z2). All metrics as shown as point estimates (95% confidence intervals).

Table S5: Multivariable linear regression model showing associations with IFI27 expression at time of contemporaneous SARS-CoV-2 positivity.

Includes 31 participants with contemporaneous PCR positivity for SARS-CoV-2. Outcome is IFI27 Z-score.

Characteristic	Beta	95% CI[1]	p-value
(Intercept)	8.4	4.3, 12	<0.001
Cycle threshold	-0.16	-0.26, -0.06	0.003
Age	0.00	-0.05, 0.05	>0.9
Sex			
Female	—	—	
Male	-0.22	-1.4, 0.98	0.7
Current symptoms	-0.39	-1.6, 0.80	0.5

[1] CI = Confidence Interval

Table S6. COVIDsortium investigators (alphabetical order)

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