# Transcriptomics of Bronchoalveolar Lavage Cells Identifies New Molecular Endotypes of Sarcoidosis - Online Supplementary Materials

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#### Supplementary Website

We have generated a supplementary website (<u>https://yale-p2med.github.io/SARC\_BAL/</u>) for this article from which data, analytical codes, paper supplement, results of supervised analysis, results of unsupervised analysis can be downloaded.

#### Sample preparation and RNA sequencing

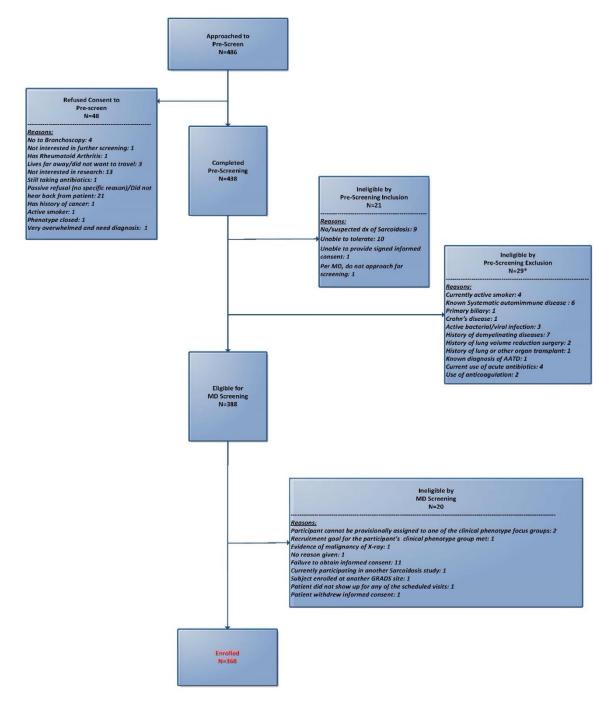
All patients involved in this study have signed a consent to participate in this study in accordance with institutional IRB protocols (Figure S1). Total RNA was extracted from BAL samples using Qiazol following Qiagen's miRNeasy protocol (Qiagen 217004) and using QiaCube. RNA guantity and guality was assessed using NanoDrop (Thermo Scientific) and TapeStation 2200 (Agilent). RNA Integrity Number (RIN) over 6.5 and yield over 1 ug of total RNA were criteria for acceptable guality to be submitted for sequencing (Table S1 and Supplemental Table E1). cDNA libraries were made from 1ug of total RNA upon Poly-A selection using Dynabeads® mRNA DIRECT™ Micro Purification Kit (Ambion 61021) and fragmentation using the AB Library Builder<sup>™</sup> System (Life Technologies 4463592) with the Ion Total RNA-Seg Kit for AB Library Builder<sup>™</sup> System (Life Technologies 4482416). The cDNA was amplified and barcoded using the Ion Xpress<sup>™</sup> RNA-Seg Barcode 1-16 Kit (Life Technologies 4475485). cDNA was loaded onto Ion PI<sup>™</sup> Chip Kit v2 BC (Life Technologies 4484270) using the Ion Chef<sup>™</sup> System (Life Technologies 4484177) with the Ion PI<sup>™</sup> IC 200 Kit (Life Technologies 4488377). Sequencing was performed using Ion Proton<sup>™</sup> System for Next-Generation Sequencing (Life Technologies 4476610) using the Ion PI<sup>™</sup> IC 200 Kit (Life Technologies 4488377) to obtain RNA-Seq depth of ~ 30 million single-end reads/sample with an average read length of 150bps. Successfully sequenced samples were samples whose cDNA libraries passed quality control and had depth of sequencing of  $\sim$  30 million single-end reads/sample.

**Table S1.** Sample filtering using RIN and RNA quality metrics.

STAGE (PHENOTYPE)	# SUBJECTS	# BAL SAMPLES with RNAs	# BAL SAMPLES PASSING QC	# SUCCESSFULLY SEQUENCED
TOTAL, n	318	261	219	215
Non-acute, Stage I, untreated	36	34	26	26
Acute Sarcoidosis, untreated	16	16	15	14
Remitting, untreated	54	48	44	42
Stage II-III, untreated	50	48	40	42
Stage II-III, treated	49	45	36	36
Stage IV, untreated	32	18	13	13
Stage IV, treated	46	23	19	19
Multi-organ	35	29	26	24

# Figure S1: Consort figure.

#### GRADS SARCOIDOSIS PROTOCOL CONSORT FIGURE



#### Sequencing Data Preprocessing

#### Data Quality Assessment

The Torrent Suite<sup>™</sup> Software (V5.0.5) was used to generate the raw sequencing bam file without alignment. These bam files were further converted into fastq files using the bam2fastx component from tophat2 (V2.0.12). The pre-alignment metrics provided in the Torrent Suite<sup>™</sup> Software run reports, including bead loading, Ion Sphere<sup>™</sup> Particle (ISP) density, total number of reads, filtering numbers, and mean read length. We used these quality thresholds provided by the company to filter out low quality sequencing runs. The samples in these low-quality sequencing runs were sequenced again.

The raw fastq files were assessed for sequencing reads quality using FastQC(1) to identify possible sequencing adapter or polymer contamination. The distribution of the base quality score along the read positions was also considered to control the quality. For this data set, all samples that pass the sequencing run filtering based on the sequencing run report passed the FastQC quality control.

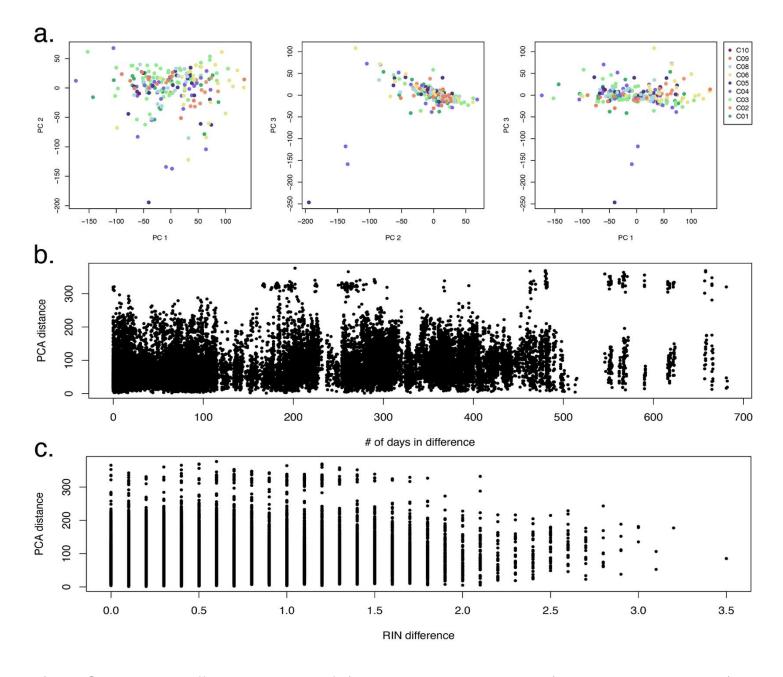
#### Mapping and FPKM Calculation

The sequencing reads in the fastq files were mapped onto the human genome (UCSC hg38) using a two-stage mapping strategy suggested by the manufacturer. In the first stage, all raw reads were mapped to hg38 using STAR (2) with gene annotation and the --b2-very-sensitive option. The unmapped reads from the first stage were further mapped to hg38 using bowtie2 (3) with local alignment and the --very-sensitive-local option. Cufflinks (4) was used to calculate the Fragments Per Kilobase of transcript per Million mapped reads (FPKMs) as the estimated gene expression levels.

#### Data Cleaning and Batch Effect Assessment

The principal component analysis (PCA) was applied to identify potential outlying sequencing reactions. There were 240 sequencing reactions for 215 samples, among which 15 reactions were identified as outliers by PCA and thus removed from further analysis. Among these 15 reactions, 11 of them also had low mapping rate, low numbers of expressed genes, and low numbers of mapped reads. For the other 4 reactions, 3 of them were shown to cluster with the PBMC samples instead of the other BAL samples, indicating that they were actually PBMC samples mislabeled as BAL samples. After the outlier removal, we had 225 high quality sequencing reactions in total, which included 31 repeated reactions from 15 BAL samples. Among the repeated reactions, we kept the one with comparable number of mapped reads to the other samples (~30 million single-end reads/sample). If multiple replicates qualified, we kept the reaction with the highest mapping rate. After this cleaning, we kept 209 sequencing reactions for 209 unique BAL samples.

In addition to data cleaning, PCA was also used to examine the data for possible batch effect due to multiple technical factors including sequencing date, sample collection centers, and the RNA integrity number (RIN). The batch effect assessment was done mainly using two ways: data visualization and the sample-sample PCA distance. To examine the effect of the sample collection center, we visualized the data using the PCA projection plot and labeled the samples based on their sample collection centers (**Figure S2a**). For the sequencing date and the RNA integrity number (RIN), we calculate the Euclidean distance between any two samples using the top 3 PCs and plotted this distance against the number of days in differences in their sequencing date and the difference in their RINs, respectively (**Figure S2b c**). None of these visualizations showed significant effect of these three technical factors.



**Figure S2**: Technical effect examination of a). sample collection center, b). sequencing date and c). RNA integrity number.

### **Supervised Analysis**

The supervised analysis identified gene signatures associated with 24 clinical traits (age, gender, race, FVC, FVC% predicted, FEV1, FEV1% predicted, DLCO, DLCO% predicted, FEV1/FVC ratio, bronchial wall thickening, bronchiectasis severity, ground glass, honeycombing, reticular

abnormality, traction bronchiectasis, mediastinal lymphadenopathy, hilar lymphadenopathy, Scadding, total BAL cell count, macrophage %, eosinophil %, lymphocyte % and neutrophil %) using non-parametric test. The Wilcoxon Rank Sum test and Kruskal-Wallis test were used for categorical clinical traits with two categories and more than two categories, respectively. The Spearman's Rho test was used for continuous clinical traits. The false discovery rate (FDR) was calculated to control for multiple testing error. Genes with an FDR<0.05 were defined to be the significant associated genes. When no genes achieve this global significance, genes with a fold change (FC) >2 and a p value<0.05 were considered as significant.

Scadding staging, PFTs% predicted, age, CT scan features with severity measurement and BAL cell differentials were considered as continuous. Race, gender, sex and CT scan features without severity measurement were considered as categorical. For disease severity, Scadding stage II, III and IV were compared to Scadding stage I separately. Similarly, all the 8 clinically defined phenotype groups were also compared to the non-acute stage I group separately. For PFTs% predicted (FEV1% predicted, DLCO% predicted, FVC% predicted), samples with PFT% predicted higher than 80% were compared to those from 50% to 80%. In addition, patients with obstructive lung disease (FEV1/FVC ratio <70%) were compared to those with restrictive lung disease (FEV1/FVC ratio <70% and FVC% predicted<80%). These separate comparisons were conducted using Wilcoxon Rank Sum test. The detailed results and the actual gene lists can be found on our supplementary website (https://yale-p2med.github.io/SARC\_BAL). The summary of the globally significant genes is presented in the Supplemental Table E2. This analysis is not adjusted for cell differentials.

The total number of significant genes associated with each clinical trait as well as the overlap between each two clinical traits is shown in Figure 2a. For the clinical traits included in the analysis, the percentage of missing values was very low (<3%). Entries on diagonal show the total number of genes significantly associated with each clinical trait and the numbers of positively (followed by +) and negative (followed by -) correlated genes for the same clinical trait. Off the diagonal, each entry

describes the total number of genes significantly associated with both given clinical traits and the number of genes with the described correlation directions for trait in the row and column in the parentheses, respectively. The GeneGo Metacore (Thomson Reuters) was applied to the lists of significant genes to identify significant (FDR<0.05) enriched pathways (Figure 2b). The detailed results and the actual gene lists can be found on our supplementary website (<u>https://yale-p2med.github.io/SARC\_BAL</u>). In Figure 2b, genes significantly associated with each clinical trait are represented by bars on the left with the length of each bar proportionate to the number of genes. These genes were further divided into positively and negatively correlated genes represented by bars in the middle with purple bars for negative correlation and yellow bars for positive correlation. The lengths of these bars are also proportionate to the number of corresponding genes. Each set of negatively or positively correlated genes was further connected to pathways (represented by bars on the right) that were significantly (FDR<0.05) enriched for genes in the given set. Only the top 5 significant (FDR<0.05) pathways with at least 3 overlapping genes are shown.

#### **Unsupervised Analysis**

The unsupervised analysis of the data consists of two parts. In the first part, we applied the WGCNA(5) to identify gene modules and assess their correlation with the following clinical traits: demographics, PFTs, CT scan variables, phenotypes, treatment and BAL cell differentials. In the second part, we chose 5 gene modules that had significant correlation (p value<0.05) with highest number of clinical traits. Genes from each module were used to cluster the patients into subgroups using K-means clustering (Figure 4). Among the identified clusters, the two extreme clusters with the largest differences in their gene expression profiles shown in Figure 4 were compared for all patient characteristics collected under GRADS study protocol for a better understanding of the clinical relevance for these modules (Supplemental Table E3). Chi-square test and Wilcoxon rank sum test were used to assess the significance for categorical and continuous patient characteristics, respectively, amongst the clusters for chosen gene modules. The MetaCore<sup>TM</sup> of GeneGO, Inc. was

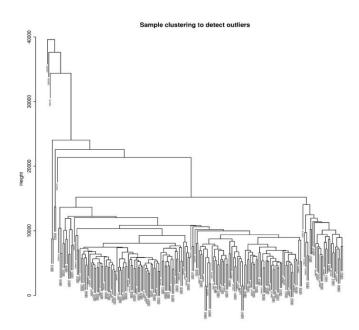
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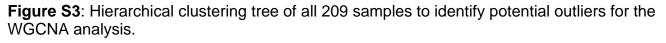
applied to identify significant enriched pathways for each gene module identified by the unsupervised analysis.

# WGCNA Analysis

# Identifying outliers

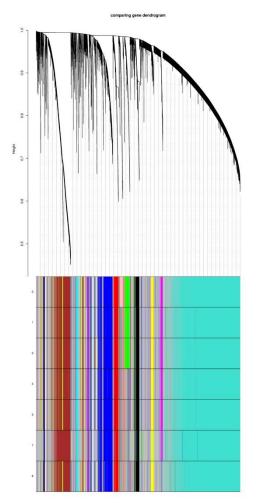
We applied the weighted gene co-expression network analysis (WGCNA) to the 209 BAL samples using the WGCNA R package (5). Genes expressed (FPKM>0.01) in less than 10% of the 209 samples





were also removed before the WGCNA analysis, which kept 22,307 genes for WGCNA analysis. The threshold chosen for the gene expression represents the minimum FPKM level that could be robustly detected by the sequencing protocol in this dataset. Since WGCNA results can be sensitive to outliers, we did hierarchical clustering of all the 209 samples using the 22,307 genes to identify possible outliers for the WGCNA analysis, which showed that there are potentially 6 branches in the tree, including 8 samples, that could have big impact on the WGCNA results (**Figure S3**). To decide exactly which samples to exclude, we applied WGCNA with trimming of 0, 1, 2, 3,..., 6 branches from the top of the

clustering tree and compared their clustering results (**Figure S4**). The comparison showed that all 6 branches have heavy impact on the WGCNA results and thus we excluded all 8 samples from further WGCNA analysis.



**Figure S4**: Comparison of the clustering results by trimming 0, 1, 2, ..., 6 branches from the top of the clustering tree in Figure S3. The dendrogram on top shows the hierarchical clustering tree of all genes by WGCNA analysis. The 7 color bars on bottom show the clustering results of all these genes after trimming off a given number of outliers (left of the color bars) in the hierarchical clustering tree of samples in Figure S3. Within each color bar, each color represents one identified gene module. The comparison between different color bars showed that when we trimmed >=8 outliers (the leftmost 8 samples in the hierarchical clustering tree in Figure S3), the clustering results became stable, justifying the need to remove 8 outliers which is consistent with observations from Figure S3.

# Correlating gene modules with clinical traits

In total, the WGCNA analysis identified 48 gene modules. The correlation between the eigen gene of

these modules and part of the clinical traits collected under the GRADS protocol is shown in Figure

**S5**. The Modules 1, 4, 18, 33 and 47 were chosen for further clustering analysis due to their significant correlation (p value<0.05) with the highest number of clinical traits or unique combination of the clinical traits. The priority was given to the modules with a largest number of genes in the module. This analysis was not adjusted for demographics, smoking, cell differentials or specific treatment because none of these had strong association with our chosen gene modules. The distribution of treatment type and the time of last treatment can be found in Table S2.

Systematic corticorsteroids												
Treatment	Currently taking	Within last 90 days but not currently	Past but not within last 90 days	Never								
Prednisone	32 (15.5%)	21 (10.1%)	94 (45.4%)	60 (29.0%)								
Medrol	0 (0%)	1 (0.5%)	9 (4.3%)	197 (95.2%)								
Dexamethasone	0 (0%)	0 (0%)	8 (3.9%)	199 (96.1%)								

Table S2. Distribution of the treatment type and the time of last treatment in GRADS cohort.

	Immune Suppressive Agents											
Treatment	Currently	Within last 90	Past but not	Never								
	taking	days but not	within last 90									
		currently	days									
Adalimumab (Humira)	5 (2.4%)	1 (0.5%)	4 (1.9%)	197 (95.2%)								
Azathioprine (Imuran)	5 (2.4%)	1 (0.5%)	6 (2.9%)	195 (94.2%)								
Chlorambucil (Leukeran)	0 (0%)	0 (0%)	1 (0.5%)	206 (99.5%)								
Colchicine	1 (0.5%)	3 (1.4%)	0 (0%)	203 (98.1%)								
Cyclophosphamide (Cytoxan)	0 (0%)	0 (0%)	2 (1.0%)	205 (99.0%)								
Cyclosporine	0 (0%)	0 (0%)	3 (1.4%)	204 (98.6%)								
(Gengraf,Neoral,Sandimmune)												
Etanercept (Enbrel)	0 (0%)	0 (0%)	3 (1.4%)	204 (98.6%)								
Hydroxychloroquine	13 (6.3%)	3 (1.4%)	17 (8.2%)	174 (84.1%)								
(Plaquinil)												
Infliximab (Remicade)	2 (0.9%)	13 (6.3%)	0 (0%)	192 (92.8%)								
IVIG	0 (0%)	0 (0%)	1 (0.5%)	206 (99.5%)								
Leflunamide (Arava)	2 (1.0%)	1 (0.5%)	4 (1.9%)	200 (96.6%)								
Methotrexate (Rheumatrex)	28 (13.5%)	4 (1.9%)	28 (13.5%)	147 (71.1%)								
Mycophenolate mofitil	7 (3.4%)	10 (4.8%)	0 (0%)	190 (91.8%)								
(CellCept)												
Pentoxyfiline (Trental)	3 (1.4%)	204 (98.6%)	0 (0%)	0 (0%)								

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Treatment	Currently taking	Within last 90 days but not currently	Past but not within last 90 days	Never
Augmentin	0 (0%)	154 (74.4%)	47 (22.7%)	6 (2.9%)
Avelox	0 (0%)	0 (0%)	16 (7.7%)	191 (92.3%)

Azithromycin	0 (0%)	15 (7.2%)	62 (30.0%)	130 (62.8%)
Bactrim DS	1 (0.5%)	4 (1.9%)	45 (21.8%)	157 (75.8%)
Ciprofloxacin	0 (0%)	3 (1.4%)	49 (23.7%)	155 (74.9%)
Clarithromycin	0 (0%)	1 (0.5%)	16 (7.7%)	190 (91.8%)
Clindamycin	0 (0%)	0 (0%)	16 (7.7%)	191 (92.3%)
Doxycycline	1 (0.5%)	4 (1.9%)	44 (21.3%)	158 (76.3%)
INH	0 (0%)	0 (0%)	4 (1.9%)	203 (98.1%)
Levaquin	0 (0%)	3 (1.5%)	29 (14.0%)	175 (84.5%)
Minocycline	0 (0%)	0 (0%)	9 (4.3%)	198 (95.7%)
Pyrazinamide	0 (0%)	0 (0%)	2 (1.0%)	205 (99.0%)
Rifampin	0 (0%)	0 (0%)	2 (1.0%)	205 (99.0%)

#### Reflux

Treatment	Currently taking	Within last 90 days but not currently	Past but not within last 90 days	Never
Aciphex (rabeprazole)	1 (0.5%)	1 (0.5%)	6 (2.9%)	199 (96.1%)
Nexium (esomeprazole)	5 (2.4%)	1 (0.5%)	38 (18.4%)	163 (78.7%)
Prevacid (lansoprazole)	4 (1.9%)	2 (1.0%)	31 (15.0%)	170 (82.1%)
Prilosec (omeprazole)	37 (17.9%)	10 (4.8%)	40 (19.3%)	120 (58.0%)
Protonix (pantoprazole)	7 (3.4%)	11 (5.3%)	0 (0%)	189 (91.3%)

#### H2 Blockers Currently Within last 90 Treatment Past but not Never taking days but not within last 90 currently days Axid (nizantidine) 0 (0%) 0 (0%) 206 (99.5%) 1 (0.5%) Pepcid (famotidine) 39 (18.8%) 2 (1.0%) 4 (1.9%) 162 (78.3%) Zantac (ranitidine) 144 (69.6%) 10 (4.8%) 6 (2.9%) 47 (22.7%)

# Inhale Steroids

Treatment	Currently taking	Within last 90 days but not currently	Past but not within last 90 days	Never
Aerobid	0 (0%)	0 (0%)	2 (1.0%)	205 (99.0%)
Advair	17 (8.2%)	8 (3.9%)	53 (25.6%)	129 (62.3%)
Azmacort	0 (0%)	0 (0%)	10 (4.8%)	197 (95.2%)
Flovent	5 (2.4%)	4 (1.9%)	42 (20.3%)	156 (75.4%)
Pulmicort	4 (1.9%)	20 (9.7%)	0 (0%)	183 (88.4%)
Serevent	1 (0.5%)	8 (3.8%)	0 (0%)	198 (95.7%)
QVAR	4 (1.9%)	12 (5.8%)	0 (0%)	191 (92.3%)

Module-trait relationships

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Module 11 (169)	-0.098 (0.2)	-0.16 (0.02)	0.13 (0.07)	-0.027 (0.7)	0.026 (0.7)	-0.041 (0.6)	0.041 (0.6)	-0.098 (0.2)	0.0023 (1)	0.036 (0.6)	-0.23 (0.001)	-0.1 (0.2)	-0.028 (0.7)	-0.088 (0.2)	-0.025 (0.7)	-0.0028 (1)	~0.029 (0.7)	0.099 (0.2)	0.014 (0.8)	0.014 (0.8)	0.087 (0.2)	-0.032 (0.7)	0.087 (0.3)	0.0027 (1)	-0.027 (0.7)	-0.1 (0.2)	-0.059 (0.5)	-0.018 (0.9)	0.12 (0.5)	
Module 7 (467)	-0.01 (0.9)	0.022 (0.8)	0.042 (0.6)	-0.1 (0.2)	-0.15 (0.04)	-0.055 (0.4)	-0.13 (0.07)	-0.094 (0.2)	-0.18 (0.01)	-0.12 (0.1)	0.13 (0.08)	0.14 (0.05)	0.12 (0.1)	0.14 (0.04)	0.14 (0.06)	-0.088 (0.2)	0.2 (0.006)	0.088 (0.2)	0.15 (0.03)	0.018 (0.8)	0.02 (0.8)	-0.28 (2e-04)	0.21 (0.005)	0.2 (0.008)	0.0077 (0.9)	0.12 (0.09)	0.048 (0.5)	0.048 (0.7)	-0.14 (0.5)	
Module 1 (7258)	0.082 (0.3)	0.046 (0.5)	-0.013 (0.9)	-0.14 (0.05)	-0.15 (0.04)	-0.11 (0.1)	-0.15 (0.03)	-0.02 (0.8)	-0.16 (0.03)	-0.094 (0.2)	0.17 (0.02)	0.088 (0.2)	0.08 (0.3)	0.097 (0.2)	0.039 (0.6)	-0.034 (0.6)	0.06 (0.4)	-0.014 (0.8)	0.21 (0.004)	0.015 (0.8)	0.028 (0.7)	0.08 (0.3)	0.0016 (1)	-0.1 (0.2)	-0.019 (0.8)	0.085 (0.2)	0.11 (0.1)	0.12 (0.3)	-0.04 (0.8)	<b>—</b> 1
Module 47 (21)	-0.03 (0.7)	0.75 (8e38)	0.065 (0.4)	0.41 (2e-09)	-0.01 (0.9)	0.53 (2e-15)	-0.014 (0.8)	0.44 (2e-10)	0.13 (0.07)	-0.19 (0.007)	0.028 (0.7)	-0.0044 (1)	0.15 (0.03)	-0.18 (0.01)	-0.014 (0.8)	-0.049 (0.5)	-0.062 (0.4)	-0.15 (0.03)	0.1 (0.2)	0.056 (0.4)	-0.081 (0.3)	-0.11 (0.2)	-0.074 (0.3)	0.12 (0.1)	0.27 (4e-04)	0.14 (0.05)	0.061 (0.4)	-0.02 (0.9)	0.04 (0.8)	
Module 37 (35)	-0.017 (0.8)	-0.064 (0.4)	-0.087 (0.2)	0.026 (0.7)	0.052 (0.5)	0.039 (0.6)	0.058 (0.4)	-0.02 (0.8)	0.081 (0.3)	-0.03 (0.7)	0.11 (0.1)	0.078 (0.3)	0.1 (0.2)	0.04 (0.6)	0.0034 (1)	0.055 (0.4)	-0.021 (0.8)	0.06 (0.4)	0.017 (0.8)	0.061 (0.4)	0.14 (0.05)	-0.19 (0.01)	-0.026 (0.7)	0.18 (0.02)	-0.012 (0.9)	-0.022 (0.8)	-0.14 (0.07)	-0.17 (0.1)	-0.21 (0.3)	
Module 43 (23)	0.12 (0.08)	-0.049 (0.5)	0.04 (0.6)	-0.12 (0.09)	-0.081 (0.3)	-0.076 (0.3)	-0.0063 (0.9)	-0.1 (0.2)	-0.074 (0.3)	-0.14 (0.04)	0.041 (0.6)	0.00025 (1)	0.13 (0.07)	0.028 (0.7)	0.059 (0.4)	0.12 (0.09)	0.026 (0.7)	0.06 (0.4)	0.05 (0.5)	0.056 (0.4)	0.029 (0.7)	-0.027 (0.7)	0.09 (0.2)	-0.029 (0.7)	0.14 (0.07)	0.073 (0.3)	0.11 (0.1)	0.14 (0.2)	-0.15 (0.4)	
Module 42 (25)	-0.0047 (0.9)	0.024 (0.7)	0.06 (0.4)	0.023 (0.7)	0.043 (0.6)	0.013 (0.9)	0.011 (0.9)	-0.03 (0.7)	-0.046 (0.5)	0.12 (0.08)	0.054 (0.4)	-0.063 (0.4)	0.046 (0.5)	-0.029 (0.7)	-0.023 (0.7)	0.071 (0.3)	0.093 (0.2)	-0.026 (0.7)	-0.044 (0.5)	0.015 (0.8)	0.013 (0.9)	-0.078 (0.3)	0.1 (0.2)	0.048 (0.5)	0.036 (0.6)	0.014 (0.8)	0.078 (0.3)	0.18 (0.1)	-0.075 (0.7)	
Module 19 (96)	-0.016 (0.8)	-0.04 (0.6)	-0.011 (0.9)	-0.068 (0.3)	-0.12 (0.1)	-0.007 (0.9)	-0.038 (0.6)	-0.078 (0.3)	-0.057 (0.4)	-0.19 (0.008)	-0.016 (0.8)	-0.024 (0.7)	0.043 (0.6)	0.12 (0.1)	0.11 (0.1)	-0.077 (0.3)	0.003 (1)	0.14 (0.05)	0.026 (0.7)	-0.034 (0.6)	-0.019 (0.8)	-0.19 (0.01)	0.23 (0.003)	0.11 (0.2)	0.038 (0.6)	-0.0076 (0.9)	-0.065 (0.4)	-0.051 (0.7)	-0.065 (0.7)	
Module 27 (66)	-0.0091 (0.9)	0.018 (0.8)	-0.091 (0.2)	-0.021 (0.8)	-0.062 (0.4)	0.043 (0.5)	0.021 (0.8)	0.038 (0.6)	0.049 (0.5)	-0.14 (0.05)	0.031 (0.7)	0.0076 (0.9)	-0.026 (0.7)	0.022 (0.8)	0.1 (0.2)	-0.023 (0.7)	-0.051 (0.5)	0.013 (0.9)	0.11 (0.1)	-0.025 (0.7)	0.022 (0.8)	-0.12 (0.1)	-0.0053 (0.9)	0.081 (0.3)	0.019 (0.8)	0.044 (0.5)	0.034 (0.7)	0.024 (0.8)	0.03 (0.9)	
Module 23 (80)	0.047 (0.5)	-0.016 (0.8)	0.074 (0.3)	-0.11 (0.1)	-0.073 (0.3)	-0.038 (0.6)	0.033 (0.7)	-0.041 (0.6)	0.026 (0.7)	-0.19 (0.007)	0.014 (0.8)	0.033 (0.6)	0.16 (0.02)	0.086 (0.2)	0.053 (0.5)	-0.021 (0.8)	0.044 (0.5)	0.014 (0.8)	-0.011 (0.9)	-0.068 (0.3)	-0.04 (0.6)	-0.0015 (1)	0.045 (0.6)	-0.045 (0.6)	-0.0075 (0.9)	-0.04 (0.6)	0.1 (0.2)	0.074 (0.5)	0.17 (0.4)	
Module 10 (174)	-0.0082 (0.9)	-0.064 (0.4)	-0.073 (0.3)	-0.16 (0.03)	-0.15 (0.03)	-0.07 (0.3)	-0.055 (0.4)	-0.13 (0.08)	-0.043 (0.6)	-0.23 (9e-04)	-0.027 (0.7)	0.068 (0.3)	0.13 (0.06)	0.13 (0.07)	0.16 (0.03)	-0.043 (0.5)	0.022 (0.8)	0.14 (0.05)	0.11 (0.1)	0.013 (0.9)	-0.032 (0.7)	-0.17 (0.03)	0.067 (0.4)	0.1 (0.2)	0.037 (0.6)	0.066 (0.4)	0.043 (0.6)	0.069 (0.6)	-0.063 (0.7)	
Module 31 (58)	0.034 (0.6)	0.097 (0.2)	-0.044 (0.5)	0.019 (0.8)	0.052 (0.5)	0.079 (0.3)	0.094 (0.2)	0.017 (0.8)	0.053 (0.5)	-0.11 (0.1)	0.021 (0.8)	0.098 (0.2)	0.14 (0.04)	0.014 (0.8)	0.019 (0.8)	0.018 (0.8)	0.055 (0.4)	-0.027 (0.7)	-0.11 (0.1)	0.048 (0.5)	0.054 (0.5)	-0.061 (0.4)	-0.014 (0.9)	0.063 (0.4)	-0.062 (0.4)	-0.054 (0.4)	-0.004 (1)	-0.056 (0.6)	0.22 (0.2)	
Module 40 (27)	0.015 (0.8)	0.056 (0.4)	-0.064 (0.4)	0.023 (0.7)	-0.0023 (1)	0.087 (0.2)	0.061 (0.4)	0.058 (0.4)	0.048 (0.5)	-0.13 (0.06)	0.15 (0.04)	0.074 (0.3)	0.14 (0.05)	0.086 (0.2)	0.05 (0.5)	0.059 (0.4)	0.098 (0.2)	0.12 (0.08)	0.15 (0.04)	0.0095 (0.9)	0.053 (0.5)	-0.086 (0.3)	0.15 (0.05)	0.085 (0.3)	-0.026 (0.7)	0.099 (0.2)	0.083 (0.3)	0.12 (0.3)	-0.14 (0.5)	
Module 22 (80)	-0.035 (0.6)	-0.03 (0.7)	-0.021 (0.8)	-0.036 (0.6)	0.04 (0.6)	-0.012 (0.9)	0.057 (0.4)	-0.043 (0.6)	0.052 (0.5)	-0.1 (0.2)	0.074 (0.3)	0.068 (0.3)	0.072 (0.3)	0.054 (0.5)	0.058 (0.4)	-0.031 (0.7)	0.015 (0.8)	-0.0016 (1)	0.0048 (0.9)	-0.0074 (0.9)	0.13 (0.07)	-0.069 (0.4)	0.056 (0.5)	0.045 (0.6)	-0.059 (0.4)	-0.042 (0.6)	0.044 (0.6)	0.07 (0.6)	0.28 (0.1)	-0.5
Module 16 (121)	0.068 (0.3)	-0.083 (0.2)	0.0025	-0.11 (0.1)	0.0075 (0.9)	-0.11 (0.1)	-0.022 (0.8)	-0.17 (0.02)	-0.12 (0.1)	-0.053 (0.5)	-0.13 (0.07)	-0.17 (0.02)	-0.027 (0.7)	0.012 (0.9)	0.021 (0.8)	-0.12 (0.09)	0.07 (0.3)	-0.0073 (0.9)	-0.053 (0.5)	-0.076 (0.3)	-0.038 (0.6)	0.01 (0.9)	0.031 (0.7)	0.017 (0.8)	0.011 (0.9)	0.059 (0.4)	0.088 (0.3)	0.017 (0.9)	0.3 (0.1)	
Module 46 (22)	-0.045 (0.5)	-0.11 (0.1)	0.045 (0.5)	-0.19 (0.008)	-0.17 (0.02)	-0.19 (0.008)	-0.14 (0.05)	-0.15 (0.05)	-0.1 (0.2)	-0.005 (0.9)	-0.043 (0.5)	0.0098 (0.9)	-0.059 (0.4)	-0.032 (0.7)	0.084 (0.2)	-0.006 (0.9)	0.027 (0.7)	0.097 (0.2)	0.0082 (0.9)	0.1 (0.1)	-0.023 (0.7)	0.013 (0.9)	0.077 (0.3)	-0.049 (0.5)	0.058 (0.5)	0.027 (0.7)	0.085 (0.3)	0.099 (0.4)	0.33 (0.07)	
Module 44 (23)	0.017 (0.8)	0.053 (0.5)	0.1 (0.2)	0.0073 (0.9)	-0.096 (0.2)	0.049 (0.5)	-0.06 (0.4)	-0.013 (0.9)	-0.079 (0.3)	-0.07 (0.3)	-0.038 (0.6)	-0.12 (0.08)	0.12 (0.1)	-0.022 (0.8)	0.032 (0.7)	0.00085 (1)	0.073 (0.3)	0.0045 (0.9)	-5.3e-05 (1)	0.029 (0.7)	-0.011 (0.9)	-0.055 (0.5)	0.024 (0.8)	0.005 (0.9)	0.07 (0.4)	0.014 (0.8)	-0.023 (0.8)	-0.0091 (0.9)	-0.018 (0.9)	
Module 39 (34)	-0.0038 (1)	0.046 (0.5)	0.016 (0.8)	0.046 (0.5)	-0.031 (0.7)	0.084 (0.2)	-0.015 (0.8)	0.033 (0.7)	0.0018 (1)	-0.095 (0.2)	0.11 (0.1)	-0.0098 (0.9)	0.076 (0.3)	0.055 (0.4)	0.064 (0.4)	0.067 (0.3)	0.04 (0.6)	0.012 (0.9)	0.069 (0.3)	0.047 (0.5)	0.041 (0.6)	-0.11 (0.2)	0.039 (0.6)	0.06 (0.4)	0.11 (0.1)	0.065 (0.4)	0.057 (0.5)	0.035 (0.8)	0.087 (0.6)	
Module 30 (61)	0.027 (0.7)	0.03 (0.7)	-0.048 (0.5)	0.017 (0.8)	-0.016 (0.8)	0.053 (0.5)	0.031 (0.7)	-0.004 (1)	0.025 (0.7)	-0.09 (0.2)	0.041 (0.6)	0.05 (0.5)	0.16 (0.02)	0.11 (0.1)	0.077 (0.3)	-0.033 (0.6)	-0.069 (0.3)	-0.037 (0.6)	0.041 (0.6)	-0.055 (0.4)	0.13 (0.08)	-0.13 (0.1)	0.034 (0.7)	0.069 (0.4)	0.089 (0.2)	-0.043 (0.5)	0.0032 (1)	0.0015 (1)	-0.1 (0.6)	
Module 26 (66)	-0.084 (0.2)	-0.081 (0.3)	0.0018	-0.1 (0.2)	-0.16 (0.03)	-0.078 (0.3)	-0.15 (0.04)	-0.16 (0.02)	-0.14 (0.05)	-0.085 (0.2)	0.093 (0.2)	0.11 (0.1)	0.15 (0.04)	0.072 (0.3)	0.22 (0.002)	-0.082 (0.3)	0.23 (0.001)	0.12 (0.08)	0.088 (0.2)	-0.025 (0.7)	0.12 (0.09)	-0.26 (5e-04)	0.12 (0.1)	0.19 (0.01)	0.044 (0.6)	0.076 (0.3)	0.17 (0.03)	0.098 (0.4)	0.21 (0.3)	
Module 48 (14)	0.029 (0.7)	0.045 (0.5)	-0.045 (0.5)	0.047 (0.5)	-0.023 (0.7)	0.089 (0.2)	0.046 (0.5)	-0.035 (0.6)	-0.0075 (0.9)	-0.087 (0.2)	-0.051 (0.5)	-0.046 (0.5)	0.031 (0.7)	0.053 (0.5)	0.0047 (0.9)	-0.058 (0.4)	0.13 (0.08)	0.098 (0.2)	0.01 (0.9)	-0.054 (0.5)	-0.027 (0.7)	-0.14 (0.06)	0.15 (0.05)	0.1 (0.2)	0.071 (0.4)	-0.069 (0.3)	0.087 (0.3)	0.17 (0.1)	0.076 (0.7)	
Module 14 (148)	0.049 (0.5)	0.049 (0.5)	-0.041 (0.6)	0.053 (0.5)	0.016 (0.8)	0.084 (0.2)	0.068 (0.4)	-0.073 (0.3)	-0.065 (0.4)	-0.032 (0.7)	0.028 (0.7)	-0.003 (1)	0.12 (0.09)	0.11 (0.1)	0.051 (0.5)	-0.012 (0.9)	0.032 (0.7)	-0.025 (0.7)	0.054 (0.5)	0.017 (0.8)	0.028 (0.7)	-0.2 (0.008)	0.096 (0.2)	0.14 (0.07)	0.12 (0.1)	0.039 (0.6)	0.025 (0.7)	-0.023 (0.8)	-0.15 (0.4)	
Module 15 (131)	-0.053 (0.5)	-0.053 (0.5)	-0.06 (0.4)	-0.053 (0.5)	-0.026 (0.7)	-0.017 (0.8)	-0.0027 (1)	-0.1 (0.2)	-0.03 (0.7)	-0.098 (0.2)	0.079 (0.3)	0.1 (0.2)	0.092 (0.2)	0.11 (0.1)	0.15 (0.04)	-0.069 (0.3)	0.081 (0.3)	0.1 (0.2)	0.092 (0.2)	-0.015 (0.8)	0.089 (0.2)	-0.3 (5e-05)	0.14 (0.07)	0.25 (8e-04)	0.082 (0.3)	0.13 (0.06)	0.035 (0.7)	-0.048 (0.7)	-0.18 (0.3)	
Module 3 (1673)	-0.0012 (1)	-0.064 (0.4)	0.081 (0.3)	-0.0079 (0.9)	-0.044 (0.5)	0.0041	-0.067 (0.4)	-0.038 (0.6)	-0.034 (0.6)	-0.022 (0.8)	0.061 (0.4)	0.17 (0.02)	0.15 (0.04)	0.00098 (1)	0.052 (0.5)	0.045 (0.5)	0.076 (0.3)	0.13 (0.07)	-0.011 (0.9)	0.011 (0.9)	0.1 (0.2)	-0.24 (0.002)	0.23 (0.003)	0.21 (0.006)	0.038 (0.6)	0.0023	-0.012 (0.9)	0.039 (0.7)	-0.12 (0.5)	
Module 9 (175)	0.01 (0.9)	-0.038 (0.6)	0.0082 (0.0)	-0.078 (0.3)	-0.062 (0.4)	-0.046 (0.5)	-0.024 (0.7)	-0.13 (0.08)	-0.055 (0.5)	-0.07 (0.3)	0.07 (0.3)	0.16 (0.02)	0.057 (0.4)	0.12 (0.1)	0.16 (0.03)	-0.075 (0.3)	0.052 (0.5)	0.048 (0.5)	0.098 (0.2)	0.038 (0.6)	0.13 (0.08)	-0.2 (0.01)	0.18 (0.02)	0.17 (0.02)	0.011 (0.9)	0.0072 (0.9)	0.017 (0.8)	0.06 (0.6)	-0.055 (0.8)	-0
Module 41 (26)	-0.035 (0.6)	-0.11 (0.1)	-0.13 (0.07)	-0.043 (0.5)	-0.021 (0.8)	-0.028 (0.7)	0.011 (0.9)	-0.1 (0.2)	-0.09 (0.2)	-0.022 (8.0)	0.13 (0.06)	0.072 (0.3)	0.12	0.034 (0.6)	0.019 (0.8)	-0.17 (0.02)	0.034 (0.6)	0.056 (0.4)	-0.053 (0.5)	-0.015 (0.8)	0.074 (0.3)	-0.055 (0.5)	0.12 (0.1)	0.041 (0.6)	-0.16 (0.03)	-0.045 (0.5)	-0.025 (0.7)	0.032 (0.8)	-0.13 (0.5)	
Module 8 (187)	-0.0051 (0.9)	-0.078 (0.3)	0.025 (0.7)	-0.1 (0.2)	-0.12 (0.1)	-0.073 (0.3)	-0.091 (0.2)	-0.17 (0.02)	-0.13 (0.07)	-0.11 (0.1)	0.095 (0.2)	0.11 (0.1)	0.12 (0.1)	0.19 (0.008)	0.15 (0.03)	-0.049 (0.5)	0.19 (0.009)	0.1 (0.2)	0.14 (0.06)	0.035 (0.6)	0.034 (0.6)	-0.32 (1e-05)	0.21 (0.006)	0.26 (7e-04)	0.11 (0.2)	0.087 (0.2)	0.062 (0.4)	0.0075 (0.9)	-0.028 (0.9)	
Module 25 (72)	-0.028 (0.7)	-0.04 (0.6)	-0.044 (0.5)	-0.051 (0.5)	-0.14 (0.06)	-0.025 (0.7)	-0.096 (0.2)	-0.078 (0.3)	-0.092 (0.2)	-0.043 (0.6)	0.089 (0.2)	0.032 (0.7)	0.033 (0.6)	0.21 (0.003)	0.22 (0.002)	0.0083 (0.9)	0.14 (0.05)	0.019 (0.8)	0.11 (0.1)	0.06 (0.4)	0.12 (0.09)	-0.23 (0.003)	0.19 (0.01)	0.17 (0.03)	0.038 (0.6)	0.14 (0.04)	0.083 (0.3)	0.044 (0.7)	-0.17 (0.4)	
Module 24 (79)	-0.028 (0.7)	-0.046 (0.5)	-0.069 (0.3)	-0.039 (0.6)	-0.094 (0.2)	0.016 (0.8)	-0.033 (0.6)	-0.056 (0.4)	-0.043 (0.6)	-0.16 (0.03)	0.18 (0.01)	0.17 (0.02)	0.09 (0.2)	0.15 (0.03)	0.14 (0.06)	-0.046 (0.5)	0.16 (0.02)	0.076 (0.3)	0.11 (0.1)	0.048 (0.5)	0,14 (0.04)	-0.34 (6e-06)	0.19 (0.01)	0.26 (7e-04)	0.13 (0.09)	0.092 (0.2)	0.028 (0.7)	-0.026 (0.8)	-0.12 (0.5)	
Module 28 (63)	0.065 (0.4)	-0.023 (0.7)	-0.025 (0.7)	-0.17 (0.02)	-0.18 (0.01)	-0.082 (0.2)	-0.12 (0.1)	-0.15 (0.03)	-0.13 (0.08)	-0.26 (3e-04)	0.024 (0.7)	0.12 (0.09)	0.041 (0.6)	0.093 (0.2)	0.21 (0.003)	0.11 (0.1)	0.065 (0.4)	0.07 (0.3)	0.16 (0.03)	-0.0035 (1)	0.088 (0.2)	-0.24 (0.001)	0.072 (0.4)	0.21 (0.006)	0.18 (0.02)	0.12 (0.08)	0.12 (0.1)	0.067 (0.6)	0.1 (0.6)	
Module 34 (44)	0.045 (0.5)	0.026 (0.7)	0.0099 (0.9)	-0.043 (0.5)	-0.03 (0.7)	-0.0017 (1)	-0.022 (0.8)	-0.055 (0.4)	-0.017 (0.8)	-0.16 (0.02)	0.027 (0.7)	0.076 (0.3)	0.12 (0.1)	-0.01 (0.9)	0.099 (0.2)	-0.06 (0.4)	-0.013 (0.9)	-0.091 (0.2)	0.01 (0.9)	-0.016 (0.8)	0.047 (0.5)	-0.09 (0.2)	0.037 (0.6)	0.05 (0.5)	0.14 (0.06)	0.037 (0.6)	0.032 (0.7)	-0.046 (0.7)	0.13 (0.5)	
Module 21 (88)	0.02 (0.8)	-0.09 (0.0)	-0.049 (0.5)	-0.098 (0.2)	-0.096 (0.2)	-0.04 (0.6)	-0.035 (0.6)	-0.15 (0.03)	-0.18 (0.01)	-0.15 (0.03)	0.068 (0.3)	0.14 (0.05)	0.092 (0.2)	0.17 (0.02)	0.22 (0.002)	-0.11 (0.1)	0.22 (0.002)	0.1 (0.2)	0.16 (0.02)	0.13 (0.07)	0.021 (0.8)	-0.38 (3e-07)	0.19 (0.01)	0.32 (1e-05)	0.19 (0.01)	0.19 (0.007)	0.049 (0.5)	0.023 (0.8)	-0.29 (0.1)	
Module 6 (504)	-0,14 (0.04)	-0.075 (0.3)	0.017 (0.8)	-0.066 (0.4)	-0.11 (0.1)	-0.027 (0.7)	-0.051 (0.5)	-0.12 (0.1)	-0.032 (0.7)	-0.088 (0.2)	-0.05 (0.5)	0.04 (0.6)	0.064 (0.4)	0.13 (0.07)	0.15 (0.03)	-0.0059 (0.9)	0.072 (0.3)	0.11 (0.1)	0.055 (0.4)	0.0046 (0.9)	0.021 (0.8)	-0.23 (0.002)	0.15 (0.06)	0.18 (0.02)	0.052 (0.5)	0.1 (0.2)	-0.015 (0.8)	-0.066 (0.6)	-0.13 (0.5)	
Module 33 (51)	0.032 (0.6)	0.0049 (0.9)	-0.05 (0.5)	0.031 (0.7)	0.017 (0.8)	0.085 (0.2)	0.045 (0.5)	-0.048 (0.5)	0.0014 (1)	-0.13 (0.06)	0.14 (0.05)	0.21 (0.003)	0.16 (0.02)	0.12 (0.1)	0.15 (0.04)	-0.022 (0.8)	0.11 (0.1)	0.0048 (0.9)	0.083 (0.2)	0.056 (0.4)	0.011 (0.9)	-0.46 (2e-10)	0.19 (0.01)	0.44 (2e-09)	0.11 (0.1)	0.088 (0.2)	-0.11 (0.2)	-0.19 (0.1)	-0.45 (0.01)	
Module 5 (559)	-0.17 (0.01)	0.039 (0.6)	0.069 (0.3)	0.13 (0.08)	0.025 (0.7)	0.14 (0.05)	0.085 (0.2)	0.011 (0.9)	0.042 (0.6)	0.058 (0.4)	-0.094 (0.2)	-0.028 (0.7)	0.02 (0.8)	0.069 (0.3)	0.031 (0.7)	0.12 (0.1)	0.018 (0.8)	0.082 (0.3)	-0.069 (0.3)	0.036 (0.6)	0.007 (0.9)	-0.11 (0.2)	0.053 (0.5)	0.093 (0.2)	-0.019 (0.8)	0.0056 (0.9)	-0.057 (0.5)	-0.009 (0.9)	-0.27 (0.1)	0.5
Module 4 (1626)	0.13 (0.07)	0.023 (0.7)	-0.045 (0.5)	-0.076 (0.3)	-0.094 (0.2)	-0.0091 (0.9)	-0.072 (0.3)	-0.096 (0.2)	-0.086 (0.2)	-0.2 (0.006)	0.23 (0.001)	0.29 (4e-05)	0.21 (0.003)	0.16 (0.02)	0.25 (5e-04)	-0.059 (0.4)	0.16 (0.02)	0.046 (0.5)	0.17 (0.02)	0.05 (0.5)	0.035 (0.6)	-0.51 (2e-12)	0.16 (0.03)	0.46 (3e-10)	0.17 (0.03)	0.19 (0.008)	-0.04 (0.6)	-0.19 (0.1)	-0.31 (0.09)	
Module 12 (169)	-0.0037 (1)	0.013 (0.9)	-0.04 (0.6)	0.0031 (1)	-0.067 (0.4)	0.053 (0.5)	-0.037 (0.6)	-0.062 (0.4)	-0.061 (0.4)	-0.13 (0.07)	0.098 (0.2)	0.16 (0.02)	0.1 (0.2)	0.14 (0.05)	0.22 (0.002)	-0.081 (0.3)	0.2 (0.006)	0.016 (0.8)	0.095 (0.2)	0.045 (0.5)	0.023 (0.7)	-0.46 (3e-10)	0.23 (0.003)	0.37 (5e-07)	0.21 (0.007)	0.14 (0.05)	0.021 (0.8)	-0.053 (0.7)	-0.17 (0.4)	
Module 13 (159)	-0.027 (0.7)	0.0022 (1)	0.075 (0.3)	-0.096 (0.2)	-0.16 (0.03)	-0.038 (0.6)	-0.11 (0.1)	-0.12 (0.1)	-0.13 (0.08)	-0.18 (0.01)	0.037 (0.6)	0.066 (0.4)	0.16 (0.03)	0.17 (0.02)	0.18 (0.01)	-0.041 (0.6)	0.21 (0.004)	0.093 (0.2)	0.15 (0.04)	0.03 (0.7)	0.14 (0.05)	-0.21 (0.007)	0.2 (0.01)	0.12 (0.1)	0.15 (0.06)	0.085 (0.2)	0.13 (0.1)	-0.058 (0.6)	0.38 (0.04)	
Module 29 (61)	0.038 (0.6)	-0.028 (0.7)	0.04 (0.6)	-0.13 (0.06)	-0.13 (0.07)	-0.12 (0.09)	-0.14 (0.05)	-0.12 (0.1)	-0.12 (0.09)	-0.0036 (1)	0.12 (0.09)	0.031 (0.7)	0.19 (0.009)	0.094 (0.2)	0.089 (0.2)	0.037 (0.6)	0.19 (0.009)	0.13 (0.07)	0.11 (0.1)	-0.021 (0.8)	0.12 (0.1)	-0.051 (0.5)	0.1 (0.2)	-0.013 (0.9)	0.047 (0.5)	0.067 (0.3)	0.074 (0.3)	-0.01 (0.9)	0.16 (0.4)	
Module 36 (40)	0.0059 (0.9)	0.0024 (1)	-0.064 (0.4)	-0.13 (0.07)	-0.16 (0.03)	-0.049 (0.5)	-0.12 (0.1)	-0.13 (0.08)	-0.13 (0.08)	-0.24 (5e-04)	0.15 (0.03)	0,11 (0.1)	0.16 (0.03)	0.18 (0.01)	0.27 (1e-04)	0.06 (0.4)	0.19 (0.007)	0.023 (0.8)	0.2 (0.005)	0.015 (0.8)	0.058 (0.4)	-0.28 (2e-04)	0.1 (0.2)	0.23 (0.002)	0.19 (0.01)	0.23 (9e-04)	0.13 (0.1)	-0.063 (0.6)	-0.0043 (I)	
Module 17 (104)	0.079 (0.3)	-0.023 (0.7)	0.12 (0.1)	-0.17 (0.02)	-0.21 (0.004)	-0.09 (0.2)	-0.14 (0.06)	-0.15 (0.03)	-0.2 (0.007)	-0.2 (0.004)	0.073 (0.3)	0.049 (0.5)	0.052 (0.5)	0.12 (0.1)	0.2 (0.005)	-0.011 (0.9)	0.32 (4e-06)	0.07 (0.3)	0.22 (0.002)	0.11 (0.1)	-0.012 (0.9)	-0.25 (0.001)	0.19 (0.01)	0.21 (0.006)	0.16 (0.04)	0.21 (0.004)	0.093 (0.2)	-0.084 (0.5)	-0.021 (0.9)	
Module 32 (53)	-0.029 (0.7)	0.015 (0.8)	0.04 (0.6)	0.033 (0.6)	0.0093 (0.9)	0.019 (0.8)	-0.022 (0.8)	-0.049 (0.5)	-0.14 (0.06)	0.067 (0.3)	0.11 (0.1)	0.09 (0.2)	-0.019 (0.8)	0.05 (0.5)	0.14 (0.06)	0.059 (0.4)	0.22 (0.002)	0.065 (0.4)	0.2 (0.006)	0.089 (0.2)	0.014 (0.8)	-0.067 (0.4)	0.18 (0.02)	0.051 (0.5)	0.19 (0.01)	0.1 (0.2)	0.089 (0.3)	-0.0083 (0.9)	0.082 (0.7)	
Module 38 (34)	0.0055 (0.9)	0.03 (0.7)	0.0032	0.024 (0.7)	0.029 (0.7)	0.082 (0.3)	0.084 (0.2)	0.016 (0.8)	0.051 (0.5)	-0.15 (0.04)	8600.0 (0.9)	0.017 (0.8)	0.12 (0.1)	0.0056 (0.9)	0.053 (0.5)	-0.0042 (1)	-0.034 (0.6)	-0.044 (0.5)	-0.063 (0.4)	0.077 (0.3)	0.071 (0.3)	-0.0098 (0.9)	-0.046 (0.6)	-0.0075 (0.9)	0.021 (0.8)	-0.012 (0.9)	-0.055 (0.5)	-0.18 (0.1)	0.15 (0.4)	
Module 35 (44)	-0.0069 (0.9)	0.016 (0.8)	-0.073 (0.3)	0.044 (0.5)	0.0017 (1)	0.075 (0.3)	0.067 (0.4)	-0.035 (0.6)	-0.0058 (0.9)	-0.12 (0.09)	-0.082 (0.3)	-0.078 (0.3)	0.037 (0.6)	0.069 (0.3)	0.097 (0.2)	0.0023 (1)	-0.051 (0.5)	0.031 (0.7)	0.035 (0.6)	-0.01 (0.9)	0.06 (0.4)	-0.15 (0.04)	0.05 (0.5)	0.076 (0.3)	0.062 (0.4)	0.012 (0.9)	0.0019 (1)	0.028 (0.8)	0.037 (0.8)	
Module 20 (94)	-0.039 (0.6)	0.0049 (0.9)	0.023 (0.7)	-0.0037 (1)	-0.02 (0.8)	0.024 (0.7)	-0.008 (0.9)	-0.063 (0.4)	-0.0065 (0.9)	-0.066 (0.4)	0.08 (0.3)	0.067 (0.3)	0.14 (0.06)	0.13 (0.07)	0.085 (0.2)	0.062 (0.4)	0.027 (0.7)	0.049 (0.5)	0.028 (0.7)	0.018 (0.8)	0.12 (0.1)	-0.094 (0.2)	0.043 (0.6)	0.053 (0.5)	0.019 (0.8)	0.065 (0.4)	0.072 (0.4)	0.028 (0.8)	0.064 (0.7)	
Module 18 (99)	-0.098 (0.2)	-0.00056 (1)	0.014 (0.8)	-0.1 (0.2)	-0.26 (2e-04)	-0.059 (0.4)	-0.23 (0.001)	-0.033 (0.7)	0.055 (0.4)	-0.15 (0.04)	0.091 (0.2)	0.045 (0.5)	0.068 (0.3)	0.079 (0.3)	0.016 (0.8)	0.1 (0.1)	0.079 (0.3)	0.083 (0.2)	-0.023 (0.8)	-0.0068 (0.9)	0.16 (0.03)	-0.18 (0.02)	0.14 (0.06)	0.12 (0.1)	0.11 (0.2)	0.011 (0.9)	0.024 (0.8)	0.035 (0.8)	0.043 (0.8)	
Module 45 (23)	0.015 (0.8)	-0.041 (0.6)	-0.08 (0.3)	-0.083 (0.2)	-0.1 (0.2)	-0.064 (0.4)	-0.11 (0.1)	-0.095 (0.2)	-0.025 (0.7)	-0.076 (0.3)	0.057 (0.4)	0.055 (0.4)	0.12 (0.1)	-0.0063 (0.9)	0.05 (0.5)	0.026 (0.7)	0.14 (0.05)	-0.093 (0.2)	0.03 (0.7)	-0.098 (0.2)	0.098 (0.2)	-0.079 (0.3)	-0.023 (0.8)	0.028 (0.7)	0.06 (0.4)	0.044 (0.5)	-0.032 (0.7)	-0.2 (0.09)	0.17 (0.4)	
Module 2 (5602)	-0.14 (0.04)	-0.0066 (0.9)	0.089 (0.2)	0.08 (0.3)	-0.021 (0.8)	0.12 (0.1)	0.071 (0.3)	-0.026 (0.7)	-0.023 (0.8)	-0.015 (0.8)	-0.097 (0.2)	0.0051 (0.9)	0.099 (0.2)	0.08 (0.3)	0.14 (0.06)	0.046 (0.5)	0.04 (0.6)	0.069 (0.3)	0.038 (0.6)	0.06 (0.4)	-0.015 (0.8)	-0.18 (0.02)	0.057 (0.5)	0.16 (0.03)	-0.032 (0.7)	0,12 (0.1)	0.039 (0.6)	0.023 (0.8)	-0.046 (0.8)	
	AGE	SER A	ACE &	EV1 Per	jited .	FNC BIRD	DICC DICC	Dello predi	UNEWC HIP	ation of the state	(0.2) athy Bronce	Microne Miles Main Miles	athicke Br	ionchiects	asis sev	pound cound of	hasson meycont allelicular	Abnorn Pi	iality Imonary	AN' BAL	SROPH F	OSINOF TY	ann N	KTE EUTROP	SCAOL TIEST	inent out	Stage Treatme	IL-III Stag	10	

**Figure S5**: Heatmap showing the correlation of the 48 identified gene modules and the given clinical traits including the demographics, PFTs, CT scan features, cell differentials and the SCADDING

staging.

#### Cluster Analysis using Chosen Modules

For each of the 5 chosen modules, we applied K-means to cluster patients using its member genes only. The optimal number of clusters were chosen based on data visualization using heatmaps and multiple internal clustering criteria calculated by the Nbclust R package including the Dunn Index, the Silhouette Index, the Calinski and Harabasz Index and the Connectivity. The clinical relevance of these identified clusters or molecular endotypes was further evaluated by correlating the clustering results to all other 2,289 clinical traits collected under the GRADS protocol, including 204 environmental factors. The Chi-square test and the Kruskal-Wallis test were used when correlating the clustering results to categorical and continuous patient characteristics, respectively. The summary of this analysis and results for each identified cluster is presented in the Supplemental Table E3.

#### **Validation Analysis**

#### Freiburg Cohort

We validated our findings using a microarray expression dataset from an independent cohort of Sarcoidosis patients from Freiburg, Germany. The consents were collected following institutional IRB protocols. Bronchoscopy with bronchoalveolar lavage was performed in these patients to obtain the BAL cells. The gene expression profile of these BAL cells was quantified using the Affymetrix Human Gene 1.0 ST Arrays. The raw data was quantile normalized using the affy R package. Principal component analysis was conducted which found no outlier samples. All the 50 samples were processed in the same batch on the same day so there is no batch effect. In total, this dataset recruited 50 sarcoidosis patients. There were 12 clinical traits recorded in both Freiburg and GRADS cohorts including Scadding staging, age, gender, PFTs, PFTs% predicted and BAL cell differentials. We were unable to obtain any CT imaging features in the Freiburg cohort and therefore these features were not validated using GRADS cohort. The PFTs% predicted values in GRADS cohort, these values were determined using the GLI reference equations (7). Our validation analysis is impacted by this difference

because the PFTs% predicted values were not directly compared for validation. Instead, we calculated the correlation of genes and gene modules with FVC% predicted and FEV1% predicted in each cohort separately and compared these correlations between the two cohorts. In addition, we assessed the correlations and associations using non-parametric approaches including Spearman correlation and Wilcoxon Rank Sun test, which are robust to such difference.

#### Validating the WGCNA results

To validate the novel molecular endotypes of sarcoidosis defined in the GRADS cohort, we cluster the patients in the Freiburg cohort using genes from each of the 5 chosen gene modules individually. The two extreme clusters (indicated in column names of Table 2 and visualized in Figure 4) were compared for each of the 12 overlapping clinical traits in Freiburg cohort, which can be considered as one type of association between the clustering results or molecular endotypes with the clinical traits. This correlation was compared between the GRADS and the Freiburg cohorts for validation in Table 2. To assess the significance of validation, we conducted hypergeometric test on the overlap of the results between the two cohorts in Table 2. The p values can be round in the column title of Table 2. Due to the small number of overlapping features (12) which corresponds to a small sample size for the hypergeometric test, we defined endotypes with a less stringent threshold (p<0.1) as significantly validated.

To remove and examine the effect of cell differentials on our validation results, we adjusted the gene expression data in GRADS and Freiburg cohorts using a linear regression model to remove the BAL cell differential effect. The adjusted gene expression was used to cluster patients in both cohorts in the same way as the unadjusted gene expression data. Clinical traits significantly associated with the identified patient clusters were also identified in both cohorts and compared for validation again in the same way as the unadjusted gene expression data. The validation results using adjusted data

(Table S3) showed that modules 47, 4, 18, and 1 were validated (hypergeometric test p<0.05), indicating the robustness of our validation to BAL cell differentials of these modules.

In addition, the significant associated clinical traits in the unadjusted data in Table 2 disappeared after the data adjustment for most endotypes except for the endotype of gender and PFT (basal). This suggests that there is a correlation between important clinical traits of Sarcoidosis and BAL cell differentials, which is consistent with the fact that BAL cell differentials are also indicative of disease severity. Therefore, by removing the cell differential effect on gene expression, we also removed the effect of clinical traits important to Sarcoidosis in the expression data. The BAL differentials should be considered as disease relevant effects instead of technical effects to avoid removing important disease effect.

#### Validating the supervised analysis results

We also applied the same supervised analysis to the 12 overlapping clinical traits that are available in both GRADS and Freiburg cohorts. For each trait, the two sets of identified associated genes were compared between the two cohorts and the significance of overlap was assessed using chi-square test. In this analysis, due to the small sample size of Freiburg cohort, we consider genes with a nominal p value<0.05 as significant genes in each cohort and only genes identified in both cohorts with the same association direction (both negatively or positively correlated) in the two cohorts were considered as overlapping genes in this analysis. We found that genes associated with Scadding, Neutrophil %, Lymphocypte %, FVC, FVC% predicted, FEV1% predicted and FEV1/FVC ratio from the two cohorts significantly overlapped (Table S4).

**Table S3**. Comparison of each endotype's association with the 12 overlapping clinical traits in GRADS and Freiburg cohorts. The p values in the column titles assess the significance of the validation based on the hypergeometric test.

	Gender	ule 47 <sup>.</sup> module 0.01)	Hi Lymphac and Lymp Inflam	lule 4 ilar Jenopathy Acute hocytic mation 0.01)	Multi involver increase resp	ule 33 organ nent with d immune oonse =1)	Chr sarco	ule 18 ronic vidosis 0.01)	Module 1 Extraocular organ involvement and PI3K activation (p<0.01)			
	GRADS Freiburg (A vs B) (A vs B) P value P value		GRADS (B vs C) P value	Freiburg (B vs C) P value	GRADS (C vs D) P value	Freiburg (B vs C) P value	GRADS (C vs D) P value	Freiburg (A vs C) P value	GRADS (A vs B) P value	Freiburg (B vs C) P value		
SCADDING	0.05	0.11	0.07	0.14	0.63	0.18	0.08	0.22	0.32	0.51		
AGE	0.98	0.59	0.38	0.56	0.79	0.29	0.05	0.31	0.06	0.60		
GENDER	5.0x10 <sup>-4</sup>	5.0x10 <sup>-4</sup>	0.68	1.00	1.00	0.68	0.51	0.42	0.36	0.77		
MACROPHAGE	0.70	0.05	0.40	0.14	4.6x10 <sup>-4</sup>	0.83	0.68	0.72	0.40	0.55		
LYMPHOCYTES	0.71	0.05	0.33	0.16	2.4x10 <sup>-4</sup>	0.81	0.75	0.91	0.30	0.55		
NEUTROPHILS	0.24	0.47	0.71	0.79	0.12	0.71	0.60	0.78	0.84	0.11		
EOSINOPHILS	0.73	0.84	0.14	0.64	0.96	0.93	0.69	0.25	0.42	0.35		
FVC	2.4x10 <sup>-13</sup>	3.0x10 <sup>-3</sup>	0.24	0.97	0.26	1.00	0.12	0.82	0.70	0.66		
FEV1	2.0x10 <sup>-8</sup>	8.0x10 <sup>-3</sup>	0.68	0.92	0.65	0.65	0.21	0.85	0.41	0.90		
FVC% predicted	0.92	0.14	0.70	0.54	0.32	.32 0.15		<b>0.04</b> 0.98		0.60		
FEV1% predicted	0.92	0.75	0.58	0.58	0.41	0.18	0.21	0.60	0.11	0.86		
FEV1/FVC ratio	0.69	0.03	0.15	0.46	8.6x10 <sup>-3</sup>	0.51	0.45	0.29	0.36	0.32		

# **Table S4**. Validation of supervised analysis for the 10overlapping clinical traits between GRADS and Freiburg cohorts.

Traits	# of associated genes (GRADS)	# of associated genes (Freiburg)	# of overlapping genes	Chi-square p value
SCADDING	2,394	1,682	431	1.2x10 <sup>-73</sup>
AGE	1,373	556	26	0.05
GENDER	1,075	409	14	0.10
Macrophage %	3,487	445	89	0.15
Eosinophil %	2,674	492	67	0.87
Neutrophil %	2,420	755	72	0.04
Lymphocyte %	5,310	300	31	3.4x10 <sup>-10</sup>
FVC% predicted	2,612	622	16	7.3x10 <sup>-15</sup>
FEV1% predicted	3,243	348	39	1.5x10 <sup>-2</sup>
FEV1/FVC ratio	1,928	375	20	6.4x10 <sup>-3</sup>

#### Genes associated with BAL macrophage and eosinophil differentials

#### Genes increasing with increased macrophage fraction in BAL

Among genes most associated (Spearman's rho > 0.2, FDR < 0.05) with increased macrophage fraction were the known alveolar macrophage markers SIGLEC11, ANXA1, ALOX5, CXCL5, ITGA5, LRP1, TREM, IRS2. Interestingly PECAM1, a known macrophage marker was among the most associated genes (Spearman's rho 0.36, FDR < 0.05) with increased macrophage fraction, potentially reflecting monocyte differentiation into macrophages and modulation of macrophage function (8). Similar to genes associated with lymphocyte differential, genes associated with decreased macrophage fraction overlapped with genes associated with increased Scadding stage (71), hilar lymphadenopathy (213), and bronchial wall thickening (254), but they also overlapped with genes associated with increased traction bronchiectasis (28) and reticular abnormalities (71) (Figure 2a) potentially reflecting unique transcriptional programs in macrophages in lung fibrosis. Among the overlapping decreased genes were SLC40A, PLXNC1, and CMKLR1 known to be involved in initiation and resolution of inflammation (9, 10). Some of the functional associations are most informative when looked at together (Figure 2b). The increase in BAL macrophages fraction was associated with an increase in development and fibrosis related pathways such as PI3K/AKT, MAPK, BMP7 and K-RAS signaling (Figure 2b, supplementary website).

# Genes decreasing with increase in eosinophil fraction in BAL are associated with increase in airway thickness

Mild increases in BAL eosinophil counts have been reported in progressive sarcoidosis (11). In our cohort, the BAL eosinophil fraction has an average of 0.24% and range from 0% to 5.5%. Out of 115 genes associated with BAL eosinophil fraction, 27 genes (9 positively and 18 negatively) were correlated with bronchial thickening and 10 were negatively correlated with reticular abnormality. CAMP, IRS2, ST3GAL2, SPIRE2, and FHL1 were negatively correlated with eosinophil counts, bronchial wall thickening and reticular abnormality. Although correlation between bronchial wall thickening and the eosinophil counts had marginal significance (p value= 0.056 and Spearman rho=0.135) in our data, common negatively correlated genes such as CAMP and IRS2 were identified. CAMP was previously shown to be decreased in severe sarcoidosis (12). Decrease in IRS2 led to pulmonary inflammation and accumulation of eosinophils in allergic lung inflammation and remodeling (13).

**Table S5**. Breakdown of patients based on PFTs% predicted severity.

PHENOTYPE GROUPS	PHENOTYPE GROUPS 1. MULTIORGAN		3. STAGE II-III TREATED	4. STAGE II-III UNTREATED	5. STAGE IV TREATED	6. STAGE IV UNTREATED	7. ACUTE UNTREATED	8. REMITTING UNTREATED	
TOTAL, n	23	25	34	42	19	12	14	40	
FEV1% PRED severity									
Mild, n (%)	21 (91.3%)	19 (76.0%)	22 (64.7%)	33 (78.6%)	7 (36.8%)	9 (75.0%)	12 (85.7%)	38 (95.0%)	
Moderate, n (%)	2 (8.7%)	3 (12.0%)	5 (14.7%)	5 (11.9%)	7 (36.8%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	
Moderately severe, n (%)	0 (0.0%)	0 (0.0%)	5 (14.7%)	1 (2.4%)	2 (10.5%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	
Severe, n (%)	0 (0.0%)	0 (0.0%)	2 (5.9%)	0 (0.0%)	3 (15.8%)	2 (16.7%)	0 (0.0%)	0 (0.0%)	
Very severe, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
NA, n (%)	0 (0.0%)	3 (12.0%)	0 (0.0%)	3 (7.1%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	1 (2.5%)	
FVC% PRED severity									
Mild, n (%)	23 (100%)	20 (80.0%)	26 (76.5%)	37 (88.1%)	11 (57.9%)	9 (75.1%)	12 (85.7%)	39 (97.5%)	
Moderate, n (%)	0 (0.0%)	2 (8.0%)	3 (8.8%)	1 (2.4%)	7 (36.8%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	
Moderately severe, n (%)	0 (0.0%)	0 (0.0%)	4 (11.8%)	1 (2.4%)	1 (5.26%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	
Severe, n (%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	
Very severe, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
NA, n (%)	0 (0.0%)	3 (12.0%)	0 (0.0%)	3 (7.1%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	1 (2.5%)	
DLCO% PRED severity									
Mild, n (%)	21 (91.3%)	21 (84.0%)	21 (61.8%)	37 (88.1%)	14 (73.7%)	9 (75.1%)	11 (78.6%)	36 (90.0%)	
Moderate, n (%)	2 (8.7%)	2 (8.0%)	8 (23.5%)	2 (4.8%)	5 (26.3%)	1 (8.3%)	1 (7.1%)	3 (7.5%)	
Severe, n (%)	0 (0.0%)	0 (0.0%)	4 (11.8%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	
NA, n (%)	0 (0.0%)	2 (8.0%)	1 (2.9%)	3 (7.1%)	0 (0.0%)	1 (8.3%)	2 (14.3%)	1 (2.5%)	

Definition of PFT severity:

FEV1% PRED and FVC% PRED: Mild (>70%), Moderate (60-69%), Moderately severe (50-59%), Severe (35-49%) and Very severe (<35%);

DLCO% PRED: Mild (>60%), Moderate (40-60%), and Severe (<40%).

# Figure S6. An overview of GRADS CT scoring forms

Name:	test2	Subject ID:	5678	Visit:	1	Sav	/e l	Jndo
Scan Type:	inspiration	Scan Date:	2/2/2012	DOB	2/2/1950			
Sarcoidosis	Staging Key Finding	gs Other Findi	ngs					
Sarcoid	dosis scoring using	inspiratory C	scan based or	Oberstein				
						-	Volume Estima	
					None	<u>1% - 33%</u>	<u>34% - 67%</u>	<u>68% - 100%</u>
T	hickening or irregular	rity of the broncl	novascular bundl	e				
Pa	arenchymal consolid	lation (including	ground-glass op	acifications)				
In	tra-parenchymal nod	lules						
S	eptal and nonseptal I	lines						
		Patholoigcal Findings						
					none	minor	moderate	severe
Fo	ocal pleural thickening	g						
			t axis > 1 cm)					

ame:	test2	Subject ID:	5678		Visit: 1		Save	Undo			
can Type:	inspiration	Scan Date:	2/2/201	2	DOB 2/	2/1950					
Sarcoidosis	Staging Key Findin	gs Other Find	lings								
Lymphad	lenopathy				Γ	Aicronodules	s (2 - 4 mm)				
Medias	tinal lymphadenopatl	hy: 💿 No	Bilatera	l ⊚ Left @	Right	Present:	No      ○ Yes				
Hilar lyr	mphadenopathy:	No	Bilatera	al ⊚ Left @	Right	Distribution	: OPerilymphatic	Peribro	nchovascu	ular 💿 Both 🛛	Random
Calcifie	ed lymph node:	No	Yes			Pattern:	Sarcoid galaxy	Sarcoid	l cluster		
Necroti	ic_Lymph_Node:	No	Yes			Conglomer	ate micronodules 💿 No	o ⊚Ye	es		
Size of	largest lymph node	(mm):									
Airway ar	nd Vasculature Dist	ortion					Airway and Va	ascular Dis	stortion D	istribution and	Pattern
Bronch	ovascular bundle dis	stortion:	No	Mild	Moderate	Severe	Cranial-cau	dal distribut	tion: 🖲 N	o 💿 Upper	Lower
Bronch	ial distortion (deform	ation of lumen	): 🔍 No	Mild	Moderate	Severe	Axial distribu	ution:	N	o © Central	Periphera
Bronch	ial wall thickening:		No	Mild	Moderate	Severe	Pattern:		© F	ocal 💿 Diffuse	
Tractio	n Bronchiectasis:		No	Mild	Moderate	Severe					
Bronch	iectasis (excluding tr	raction):	No	Mild	Moderate	Severe					
Parench	yma Opacity and Di	stortion									
-	l glass:		Mild	Moderate	Severe		Pleural effusion:	No	Mild	Moderate	Severe
	combing:		Mild	<ul> <li>Moderate</li> </ul>	© Severe		Pleural thickening:	No	⊚ Mild	Moderate	<ul> <li>Severe</li> </ul>
-	ar abnormality:		Mild	Moderate			Pleural calcification:	No	Mild	Moderate	<ul> <li>Severe</li> </ul>
	changes:		Mild	<ul> <li>Moderate</li> </ul>			UIP fibrosis:	No	Mild	Moderate	<ul> <li>Severe</li> </ul>
-	lidation:		Mild	Moderate	Severe		Mycetoma:	No	© Yes	~	-
Mosaic	attenuation:	No	Mild	Moderate	Severe		Interstitial Pneumonia:	No	ves		
Interlob	ular septal thickening	g: 💿 No	Mild	Moderate	Severe						
Parenchy	yma Opacity and Di	stortion Distri	ibution an	d Pattern							
Cranial	-caudal distribution:	● No	Jpper 🔘	Lower							
Axial di	stribution:	No	Central 🔘	Peripheral							
Pattern		© Focal ©[	Diffuse								

Name:	test2	Subject ID:	5678	Vis	it: 1	Save	Undo	
Scan Type:	inspiration	Scan Date:	2/2/2012	DO	B 2/2/1950			
Sarcoidosis	Staging Key Find	lings Other Findi	ngs					
Severity of	f emphysema :				Noncalcified no	odules:	Yes	No
	ions: Score empl core each segme		from the i	nspiratory CT	Number of	f nodules:	wit loop than 6	Mara than 6
		Right	Le	eft	⊚ 1			More than 6
a. L	Jpper lobe: No	ne	▼ None	•	Long axis m largest nodu	easurement of le in mm:		
	liddle lobe: No		None	•	Short axis m largest nodu	neasurement of ule in mm:		
		None	None	•	Are any node	ules calcified:	© Yes	No
	audal distribution				Are any node	ules cavitating:	Yes	No
	oper predominant	C Lower pre		Diffuse	Description	of nodule borde	rs: © Smooth	Irregular
Descript	tion of emphysem	ia :			Cavitary lesion	1:	Yes	No
a. Bu	ılla(e):		Yes	No	lf yes, num	nber of cavitary l	esions:	
b. Ce	entrilobular:		Yes	No	⊚ 1	More than 1 k	out less than 6 🛛 💿	More than 6
c. Di	stal acinar or para	septal:	Yes	No				
d. Pa	anlobular:		Yes	No	Other findings:			
Lobar or S	egmental collaps	e:	Yes	No				
Pulmonary	artery enlargeme	ent:	Yes	No				
lf Yes	, specify diameter	in mm:						
Tree-in-bu	d:		Yes	No				
Evidence of	of prior thoracic s	surgery	Yes	No				

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