ONLINE DATA SUPPLEMENT:

Radiomic Measures from Chest HRCT Associated with Lung Function in Sarcoidosis

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Section E1. Study Populations and Data Acquisition

The sarcoidosis population used in this study was recruited at National Jewish Health (NJH) as part of the NHLBI funded Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study. The GRADS study is a multi-center, observational cohort exploring the role of the microbiome and genome in subjects with Alpha-1 Antitrypsin Deficiency and/or Sarcoidosis[1]. Subjects were eligible for GRADS if they were between the ages of 18 and 85 years, had a confirmed diagnosis of sarcoidosis via biopsy or manifestations consistent with acute sarcoidosis (Lofgren's syndrome), met one of the nine study phenotypes and provided signed informed consent. As part of GRADS, uniform clinical data was obtained including pulmonary function testing (PFT, including pre-bronchodilator (BD) forced expiratory volume at one second (FEV1), forced vital capacity (FVC), and diffusing capacity of the lungs for carbon monoxide (DLCO)), a chest radiograph (for Scadding staging classification), and a research chest HRCT based on the COPDGene protocol[2]. Of 79 GRADS sarcoidosis subjects enrolled at NJH, N=73 subjects with a HRCT usable for quantitative analysis were used in this study. Research chest HRCTs used in this study were acquired using Siemens SOMATOM Definition (N=22) or Siemens SOMATOM Definition AS+ (N=51), with the participants in the supine position during breath holding at end inspiration, and the following parameters: 120 kVp, effective tube current average 180-330 mA (varied by BMI), 500 msec exposure time, standard B35f kernel, 0.75 mm thickness, and computed interval of 0.5 mm[1].

A non-smoking, healthy control population was obtained from the COPDGene study. COPDGene is a cross-sectional prospective cohort exploring epidemiological and

genetic characteristics in smokers with and without chronic obstructive pulmonary disease[3]. A total of 108 healthy nonsmokers were recruited for COPDGene that were between the ages of 45 and 80 years, with no history of lung disease and normal postbronchodilator spirometry[2]. As part of COPDGene, uniform clinical data was obtained including PFT (spirometry and lung volumes) and a research chest HRCT. As DLCO was not collected in COPDGene, it was not used as an outcome in this study. Of 108 COPDGene non-smoking healthy controls, N=78 subjects were included in the present study who had a HRCT acquired using Siemens SOMATOM Definition (N=45), Siemens SOMATOM Definition Flash (N=25), Siemens SOMATOM Definition AS+ (N=6) or Siemens SOMATOM Sensation 64 (N=2). These HRCT had the same parameters as GRADS, except for a tube current average of 400 mA; according to Mackin[4], we do not believe that this difference in tube current affected our radiomic results.

Section E2. Data-Processing

Each CT scan had the same axial slice thickness (0.750mm) and interval (0.500mm); however, since a 512x512 image matrix was used for the reconstruction, the spacing in the coronal and sagittal planes were dependent on the size of the subject. To remove spacing variability across subjects and anatomical planes, all scans were resampled to 1x1x1 mm^3 spacing. A thresholding- and region-based segmentation technique, as implemented in the `lungct` R package, was used to segment the left and right lung from the resampled scans. CT scans were further thresholded at HU<0 to remove non-lung tissue found on the boundaries of the masked CT. Masked CT slices with less than

2,000 pixels (approximately 5% or less of the masked slice) were discarded due to small image size and unstable estimates; this resulted in the removal of approximately 15% of slices per person.

Section E3. Radiomic Measures

Radiomics can be divided into first and second order measures. First order measures quantify features of the distribution of the Hounsfield unit (HU) pixel values, such as the mean, median, standard deviation, skewness and kurtosis, among others[5]. Second order measures quantify spatial smoothness or associations between adjacent pixels. Examples include grey-level co-occurrence matrices (GLCMs), grey-level run-length matrices (GLRLMs), fractal dimension, Moran's I and Geary's C, among others[5]. Typical radiomic analyses investigate a large number of radiomic features by using a validation procedure, whereby a subset of the data is used to select important radiomic features, and an additional subset of the data is used to evaluate the selected radiomic features[6]. However, this approach requires a large amount of data[7]. Given our moderate sample size (N=151) and to avoid the problem of false positive findings, we have pre-selected five radiomic features that we hypothesize will be useful to differentiate sarcoidosis and control groups.

From the first-order measures, we selected skewness and kurtosis as both measure the non-normality of the distribution which we observe in lung CTs (Figure 1); additionally, both have been shown to be successful for idiopathic pulmonary fibrosis[8], a disease which results in increased opacification on CT scans, similar to sarcoidosis. Since sarcoidosis results in increased opacification (i.e. whiter regions) on HRCT from

parenchymal abnormalities (such as micronodules, conglomerate masses, fibrosis and other radiographic patterns), we hypothesized that there would be less skewness and less kurtosis in sarcoidosis subjects as compared to controls; that is, we hypothesize that the increased opacification on the CT scans from sarcoidosis subjects will alter the HU distribution to appear more normally distributed (Figure 1; Table 1).

From the second-order measures, we pre-selected fractal dimension[9], Moran's I[10] and Geary's C[11] as all measure the spatial smoothness of the data, where smoothness is defined as adjacent pixels appearing more similar, which we observe in lung CTs (Figure 1); further, these spatial summaries have shown to be very useful in detecting lung nodules[12,13]. Lower values of fractal dimension and Geary's C, and higher values of Moran's I are indicative of more smoothness. Since sarcoidosis involves the formation of micronodules in the lung that begin to conglomerate as disease worsens and/or fibrosis may develop, we hypothesized that there would be lower fractal dimension, lower Geary's C, and higher Moran's I in sarcoidosis subjects as compared to controls, since the aggregation of nodules (conglomerate masses) will result in adjacent pixels appearing more similar on a CT scan (Figure 1; Table 1).

Fractal dimension was estimated using the line transect madogram estimator for spatial data (27). Moran's I and Geary's C were estimated using an eight-nearest neighbor adjacency matrix. Mathematical representations of these measures can be found in Table 1. All measures were calculated using the `lungct` R package.

Section E4. Statistical Analysis

Demographics. Descriptive statistics (e.g. mean and standard deviation for continuous variables; frequency tables for categorical variables) were used to summarize demographic and spirometry data. To test for an association between disease group and gender, a Chi-square test was used. To test for an association between disease group and race (white/non-white), a Fisher's exact test was used, due to small cell sample sizes. Linear regression models were used to test for differences in means for all continuous variables between sarcoidosis and healthy controls, and between Scadding stages. Continuous variables include age at consent, BMI, pre-BD FEV1, pre-BD FVC, and FEV1:FVC.

Differences in Global Radiomics between Sarcoidosis and Controls. Each radiomic measure was computed on every third slice for every subject in each of the two lungs and three anatomical planes. To arrive at a single “global” value, the median value across each subject, lung and orientation were computed. Descriptive statistics (e.g. means and standard deviations) were used to summarize the global radiomic measures between disease groups. Linear regression models were used to test for differences in global radiomic measures between sarcoidosis and healthy controls, adjusted for age, gender, and BMI.

Associations between Global Radiomic Measures and Lung Function. To evaluate the difference in disease (i.e. sarcoidosis vs. control) on the association between lung function and global radiomic measures, linear regression was used with an interaction between disease group and global radiomic measures. When the effect of disease group was significant, the association between global radiomic measure and lung function is reported (estimates, standard errors, and p-values) separately by the

specific disease; otherwise, the interaction was removed, and the association is reported over all participants.

Differences in Spatial Radiomics between Sarcoidosis and Controls. We also analyzed the curve of radiomic measures throughout the lung that results from the computation of radiomic measures on each slice in both the right and left lung in each of the three anatomical orientations. Functional regression was used to determine whether there is a spatially-varying association between subjects with and without sarcoidosis on each radiomic measure; that is, whether certain regions of the lung were more different between sarcoidosis and control than other regions. We used penalized smoothing splines for our functional data analysis. The optimal degrees of freedom for the penalized smoothing spline was determined using the corrected Akaike Information Criteria (cAIC)[14]. The functional regression was adjusted for gender, age, and BMI. Standard errors and 95% confidence intervals were obtained from 1000 bootstrapped samples. The t-statistic was computed using the absolute value of the difference between sarcoidosis and healthy controls divided by the standard error at each slice percentage.

Comparisons between Scadding Stage. In sarcoidosis subjects, linear regression models were used to test for differences in global radiomic measures between Scadding stages, adjusted for age, gender, and BMI. If a significant difference was found in Scadding stage, pairwise comparisons were performed, with significance defined as $p<0.005$ for multiple comparisons (10 different combinations of pairwise differences between Scadding stages). Linear regression models were also used to estimate the amount of variance in lung function explained (i.e. adjusted r-squared) by Scadding

stage versus a combination of global radiomic measures. Step-wise regression based on AIC was used to determine which combination of global radiomic measures resulted in best model fit. Finally, functional regression using penalized smoothing splines were used to summarize radiomic measures throughout the lung between Scadding stages. Due to small sample sizes and low power, only mean estimates by Scadding stage are reported.

Analyses were independently performed for radiomic measures of skewness, kurtosis, fractal dimension, Moran's I, and Geary's C. All analyses were performed in Rstudio v1.0.136. Results were considered significant at a $p < 0.05$.

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TABLES

Table E1. Differences in global radiomic features between pulmonary sarcoidosis and Scadding stage. P-values are adjusted for gender, age, and BMI. Global radiomic features are calculated from global values across the **left** lung. Values are summarized by mean (standard error). Fractal D = fractal dimension.

		Control	Sarcoidosis	P-value	Stage 0	Stage I	Stage II	Stage III	Stage IV	P-value
		(N = 78)	(N = 73)		(N = 9)	(N = 8)	(N = 28)	(N = 11)	(N = 17)	
Axial	Skewness	3.642 (0.060)	3.166 (0.085)	<0.001	3.009 (0.131)	3.491 (0.198)	3.309 (0.150)	3.373 (0.187)	2.727 (0.172)	0.027
	Kurtosis	16.653 (0.600)	12.732 (0.688)	<0.001	10.879 (1.102)	15.052 (2.003)	14.084 (1.259)	14.248 (1.741)	9.413 (1.066)	0.032
	Fractal D	2.429 (0.003)	2.404 (0.004)	<0.001	2.434 (0.011)	2.437 (0.006)	2.397 (0.004)	2.421 (0.005)	2.374 (0.008)	<0.001
	Moran's I	0.691 (0.004)	0.702 (0.005)	0.047	0.667 (0.013)	0.668 (0.013)	0.715 (0.005)	0.680 (0.007)	0.729 (0.008)	<0.001
	Geary's C	0.226 (0.002)	0.212 (0.002)	<0.001	0.226 (0.006)	0.227 (0.005)	0.208 (0.003)	0.229 (0.005)	0.195 (0.002)	<0.001
Coronal	Skewness	3.576 (0.058)	3.115 (0.082)	<0.001	2.945 (0.120)	3.441 (0.194)	3.261 (0.146)	3.337 (0.176)	2.668 (0.166)	0.016
	Kurtosis	16.133 (0.588)	12.349 (0.677)	<0.001	10.335 (1.045)	14.433 (1.903)	13.739 (1.285)	13.955 (1.649)	9.106 (0.958)	0.03
	Fractal D	2.450 (0.003)	2.434 (0.004)	<0.001	2.458 (0.009)	2.460 (0.007)	2.428 (0.004)	2.453 (0.006)	2.404 (0.009)	<0.001
	Moran's I	0.688 (0.004)	0.700 (0.004)	0.01	0.666 (0.012)	0.674 (0.012)	0.711 (0.005)	0.673 (0.008)	0.729 (0.008)	<0.001
	Geary's C	0.235 (0.003)	0.220 (0.003)	<0.001	0.232 (0.009)	0.229 (0.006)	0.219 (0.005)	0.239 (0.006)	0.199 (0.005)	<0.001
Sagittal	Skewness	3.360 (0.054)	2.986 (0.076)	<0.001	2.843 (0.122)	3.272 (0.161)	3.120 (0.129)	3.201 (0.155)	2.567 (0.169)	0.014
	Kurtosis	14.626 (0.567)	11.605 (0.650)	<0.001	9.768 (1.057)	13.578 (1.842)	12.968 (1.188)	13.377 (1.665)	8.257 (0.944)	0.017
	Fractal D	2.478 (0.004)	2.454 (0.005)	<0.001	2.491 (0.015)	2.479 (0.007)	2.449 (0.006)	2.470 (0.008)	2.420 (0.012)	<0.001
	Moran's I	0.684 (0.003)	0.705 (0.004)	<0.001	0.671 (0.010)	0.676 (0.010)	0.715 (0.004)	0.682 (0.005)	0.736 (0.009)	<0.001
	Geary's C	0.239 (0.004)	0.214 (0.004)	<0.001	0.227 (0.009)	0.222 (0.007)	0.215 (0.006)	0.233 (0.010)	0.191 (0.005)	0.002

Table E2. Differences in global radiomic features between pulmonary sarcoidosis and Scadding stage. P-values are adjusted for gender, age, and BMI. Global radiomic features are calculated from global values across the **right** lung. Values are summarized by mean (standard error). Fractal D = fractal dimension.

		Control	Sarcoidosis	P-value	Stage 0	Stage I	Stage II	Stage III	Stage IV	P-value
		N = 78	N = 73		N = 9	N = 8	N = 28	N = 11	N = 17	
Axial	**Skewness**	3.725 (0.060)	3.181 (0.077)	<0.001	3.150 (0.127)	3.611 (0.200)	3.263 (0.139)	3.435 (0.182)	2.695 (0.114)	0.002
	Kurtosis	17.432 (0.600)	12.839 (0.673)	<0.001	12.007 (1.060)	16.197 (2.091)	13.644 (1.193)	14.888 (1.754)	9.046 (0.933)	0.007
	Fractal D	2.433 (0.003)	2.406 (0.004)	<0.001	2.437 (0.011)	2.439 (0.006)	2.396 (0.004)	2.423 (0.006)	2.380 (0.007)	<0.001
	Moran's I	0.685 (0.004)	0.701 (0.005)	0.003	0.661 (0.015)	0.665 (0.011)	0.715 (0.006)	0.682 (0.008)	0.730 (0.006)	<0.001
	Geary's C	0.232 (0.002)	0.214 (0.002)	<0.001	0.230 (0.006)	0.232 (0.005)	0.209 (0.003)	0.230 (0.005)	0.194 (0.003)	<0.001
Coronal	**Skewness**	3.700 (0.055)	3.172 (0.075)	<0.001	3.103 (0.117)	3.532 (0.198)	3.247 (0.139)	3.433 (0.158)	2.747 (0.123)	0.009
	Kurtosis	17.110 (0.552)	12.770 (0.656)	<0.001	11.591 (0.991)	15.398 (1.984)	13.736 (1.221)	14.590 (1.471)	9.390 (1.023)	0.022
	Fractal D	2.452 (0.003)	2.435 (0.004)	<0.001	2.463 (0.011)	2.459 (0.006)	2.425 (0.004)	2.453 (0.007)	2.411 (0.007)	<0.001
	Moran's I	0.684 (0.003)	0.699 (0.005)	0.001	0.659 (0.013)	0.670 (0.012)	0.712 (0.005)	0.674 (0.009)	0.727 (0.008)	<0.001
	Geary's C	0.238 (0.002)	0.220 (0.003)	<0.001	0.236 (0.006)	0.233 (0.006)	0.217 (0.005)	0.236 (0.006)	0.199 (0.005)	<0.001
Sagittal	**Skewness**	3.449 (0.054)	2.998 (0.069)	<0.001	2.915 (0.120)	3.360 (0.174)	3.092 (0.123)	3.209 (0.157)	2.578 (0.109)	0.003
	Kurtosis	15.261 (0.561)	11.404 (0.613)	<0.001	10.422 (1.102)	14.025 (1.974)	12.450 (1.084)	13.150 (1.604)	7.837 (0.756)	0.006
	Fractal D	2.483 (0.004)	2.457 (0.005)	<0.001	2.500 (0.015)	2.485 (0.008)	2.447 (0.005)	2.474 (0.009)	2.426 (0.009)	<0.001
	Moran's I	0.675 (0.003)	0.701 (0.005)	<0.001	0.658 (0.012)	0.657 (0.009)	0.712 (0.005)	0.681 (0.008)	0.738 (0.007)	<0.001
	Geary's C	0.246 (0.004)	0.221 (0.004)	<0.001	0.239 (0.010)	0.236 (0.008)	0.222 (0.006)	0.233 (0.007)	0.193 (0.006)	<0.001

Table E3. Effect of disease group on the association between lung function and global radiomic features from the left lung, adjusted for gender, age, and BMI. FEV1 = pre-bronchodilator forced expiratory volume at one second. FVC = pre-bronchodilator forced vital capacity. FractalD = fractal dimension.

Position	Outcome	Variable	P-value of difference	Effect of Sarcoidosis	Effect of Control	Effect of both groups	Adjusted R-sq
Axial	FEV1	Skewness	0.056	--	--	0.353 SE=0.078 p<0.001	0.549
Axial	FEV1	Kurtosis	0.032	0.053 SE=0.012 p<0.001	0.017 SE=0.013 p=0.189	--	0.548
Axial	FEV1	FractalD	0.001	9.251 SE=2.217 p<0.001	-1.762 SE=2.846 p=0.537	--	0.54
Axial	FEV1	Moran's I	0.011	-3.681 SE=1.949 p=0.061	3.220 SE=1.895 p=0.091	--	0.504
Axial	FEV1	Geary's C	<0.001	15.711 SE=3.629 p<0.001	-10.928 SE=4.475 p=0.016	--	0.561
Axial	FVC	Skewness	0.127	--	--	0.428 SE=0.094 p<0.001	0.593
Axial	FVC	Kurtosis	0.113	--	--	0.045 SE=0.011 p<0.001	0.585
Axial	FVC	FractalD	0.014	8.566 SE=2.749 p=0.002	-1.850 SE=3.529 p=0.601	--	0.564
Axial	FVC	Moran's I	0.007	-3.166 SE=2.343 p=0.179	5.696 SE=2.279 p=0.014	--	0.557
Axial	FVC	Geary's C	0.002	12.440 SE=4.603 p=0.008	-9.735 SE=5.676 p=0.089	--	0.564
Axial	FEV1:FVC	Skewness	0.171	--	--	0.007 SE=0.010 p=0.478	0.057
Axial	FEV1:FVC	Kurtosis	0.087	--	--	0.000 SE=0.001 p=0.712	0.054
Axial	FEV1:FVC	FractalD	0.016	0.879 SE=0.264 p=0.001	-0.097 SE=0.339 p=0.776	--	0.121
Axial	FEV1:FVC	Moran's I	0.381	--	--	-0.418 SE=0.160 p=0.010	0.097

Axial	FEV1:FVC	Geary's C	<0.001	2.114 SE=0.415 p<0.001	-1.063 SE=0.512 p=0.040	--	0.221
Coronal	FEV1	Skewness	0.042	0.497 SE=0.094 p<0.001	0.180 SE=0.130 p=0.167	--	0.569
Coronal	FEV1	Kurtosis	0.023	0.057 SE=0.012 p<0.001	0.018 SE=0.013 p=0.158	--	0.557
Coronal	FEV1	FractalD	<0.001	11.147 SE=2.157 p<0.001	-1.625 SE=2.782 p=0.560	--	0.567
Coronal	FEV1	Moran's I	<0.001	-6.190 SE=2.054 p=0.003	4.347 SE=2.184 p=0.049	--	0.527
Coronal	FEV1	Geary's C	<0.001	12.526 SE=2.631 p<0.001	-1.913 SE=2.809 p=0.497	--	0.556
Coronal	FVC	Skewness	0.127	--	--	0.470 SE=0.096 p<0.001	0.602
Coronal	FVC	Kurtosis	0.106	--	--	0.049 SE=0.011 p<0.001	0.591
Coronal	FVC	FractalD	0.002	10.551 SE=2.703 p<0.001	-2.479 SE=3.486 p=0.478	--	0.581
Coronal	FVC	Moran's I	0.001	-4.481 SE=2.500 p=0.075	7.507 SE=2.659 p=0.005	--	0.568
Coronal	FVC	Geary's C	0.043	9.190 SE=3.353 p=0.007	-0.366 SE=3.580 p=0.919	--	0.555
Coronal	FEV1:FVC	Skewness	0.108	--	--	0.009 SE=0.010 p=0.369	0.059
Coronal	FEV1:FVC	Kurtosis	0.063	--	--	0.001 SE=0.001 p=0.647	0.055
Coronal	FEV1:FVC	FractalD	0.034	0.968 SE=0.263 p<0.001	0.109 SE=0.339 p=0.748	--	0.131
Coronal	FEV1:FVC	Moran's I	0.069	--	--	-0.686 SE=0.179 p<0.001	0.142
Coronal	FEV1:FVC	Geary's C	<0.001	1.627 SE=0.298 p<0.001	-0.430 SE=0.318 p=0.178	--	0.23
Sagittal	FEV1	Skewness	0.042	0.510 SE=0.104 p<0.001	0.166 SE=0.139 p=0.235	--	0.558
Sagittal	FEV1	Kurtosis	0.027	0.056 SE=0.012 p<0.001	0.017 SE=0.013 p=0.218	--	0.548

Sagittal	FEV1	FractalD	<0.001	9.363 SE=1.743 p<0.001	0.332 SE=2.033 p=0.870	--	0.571
Sagittal	FEV1	Moran's I	<0.001	-8.043 SE=2.123 p<0.001	5.048 SE=2.741 p=0.068	--	0.541
Sagittal	FEV1	Geary's C	<0.001	10.366 SE=2.209 p<0.001	0.083 SE=2.005 p=0.967	--	0.551
Sagittal	FVC	Skewness	0.115	--	--	0.478 SE=0.105 p<0.001	0.593
Sagittal	FVC	Kurtosis	0.13	--	--	0.048 SE=0.012 p<0.001	0.585
Sagittal	FVC	FractalD	0.009	8.971 SE=2.192 p<0.001	0.970 SE=2.556 p=0.705	--	0.581
Sagittal	FVC	Moran's I	<0.001	-6.323 SE=2.613 p=0.017	8.582 SE=3.374 p=0.012	--	0.571
Sagittal	FVC	Geary's C	0.102	--	--	4.670 SE=1.962 p=0.019	0.552
Sagittal	FEV1:FVC	Skewness	0.124	--	--	0.006 SE=0.011 p=0.553	0.056
Sagittal	FEV1:FVC	Kurtosis	0.047	0.002 SE=0.002 p=0.162	-0.002 SE=0.002 p=0.195	--	0.073
Sagittal	FEV1:FVC	FractalD	0.004	0.781 SE=0.213 p<0.001	-0.071 SE=0.248 p=0.776	--	0.136
Sagittal	FEV1:FVC	Moran's I	0.035	-1.180 SE=0.243 p<0.001	-0.364 SE=0.313 p=0.248	--	0.188
Sagittal	FEV1:FVC	Geary's C	<0.001	1.334 SE=0.248 p<0.001	-0.405 SE=0.225 p=0.075	--	0.232

Table E4. Effect of disease group on the association between lung function and global radiomic features from the right lung, adjusted for gender, age, and BMI. FEV1 = pre-bronchodilator forced expiratory volume at one second. FVC = pre-bronchodilator forced vital capacity. Fractal D = fractal dimension.

Position	Outcome	Variable	P-value of difference	Effect of Sarcoidosis p-value	Effect of Control P-value	Effect of both groups	Adjusted R-sq
Axial	FEV1	Skewness	0.006	0.593 SE=0.099 p<0.001	0.170 SE=0.122 p=0.168	--	0.588
Axial	FEV1	Kurtosis	0.007	0.063 SE=0.012 p<0.001	0.018 SE=0.012 p=0.150	--	0.571
Axial	FEV1	FractalD	0.001	10.610 SE=2.344 p<0.001	-1.299 SE=3.046 p=0.671	--	0.549
Axial	FEV1	Moran's I	0.008	-4.250 SE=1.907 p=0.027	2.609 SE=1.781 p=0.145	--	0.506
Axial	FEV1	Geary's C	<0.001	15.915 SE=3.301 p<0.001	-7.303 SE=4.122 p=0.079	--	0.564
Axial	FVC	Skewness	0.041	0.645 SE=0.122 p<0.001	0.261 SE=0.151 p=0.086	--	0.613
Axial	FVC	Kurtosis	0.054	--	--	0.050 SE=0.011 p<0.001	0.594
Axial	FVC	FractalD	0.019	8.776 SE=2.947 p=0.003	-1.810 SE=3.830 p=0.637	--	0.559
Axial	FVC	Moran's I	0.012	-3.342 SE=2.310 p=0.150	4.590 SE=2.158 p=0.035	--	0.553
Axial	FVC	Geary's C	0.01	12.459 SE=4.216 p=0.004	-4.887 SE=5.265 p=0.355	--	0.561
Axial	FEV1:FVC	Skewness	0.026	0.032 SE=0.013 p=0.013	-0.012 SE=0.016 p=0.458	--	0.094
Axial	FEV1:FVC	Kurtosis	0.021	0.003 SE=0.001 p=0.028	-0.001 SE=0.002 p=0.337	--	0.088
Axial	FEV1:FVC	FractalD	0.007	1.211 SE=0.275 p<0.001	0.065 SE=0.357 p=0.856	--	0.164
Axial	FEV1:FVC	Moran's I	0.143	--	--	-0.426 SE=0.153 p=0.006	0.102

Axial	FEV1:FVC	Geary's C	<0.001	2.044 SE=0.374 p<0.001	-1.043 SE=0.468 p=0.027	--	0.241
Coronal	FEV1	Skewness	0.012	0.618 SE=0.101 p<0.001	0.207 SE=0.134 p=0.126	--	0.593
Coronal	FEV1	Kurtosis	0.01	0.065 SE=0.012 p<0.001	0.021 SE=0.013 p=0.128	--	0.575
Coronal	FEV1	FractalD	<0.001	12.481 SE=2.379 p<0.001	-0.556 SE=3.040 p=0.855	--	0.569
Coronal	FEV1	Moran's I	0.003	-5.142 SE=2.053 p=0.013	3.794 SE=2.289 p=0.100	--	0.514
Coronal	FEV1	Geary's C	0.002	10.426 SE=2.783 p<0.001	-3.417 SE=3.521 p=0.333	--	0.532
Coronal	FVC	Skewness	0.054	--	--	0.568 SE=0.103 p<0.001	0.616
Coronal	FVC	Kurtosis	0.056	--	--	0.057 SE=0.011 p<0.001	0.604
Coronal	FVC	FractalD	0.004	11.165 SE=3.002 p<0.001	-1.611 SE=3.836 p=0.675	--	0.576
Coronal	FVC	Moran's I	0.004	-3.360 SE=2.488 p=0.179	7.136 SE=2.774 p=0.011	--	0.559
Coronal	FVC	Geary's C	0.109	--	--	3.899 SE=2.863 p=0.175	0.54
Coronal	FEV1:FVC	Skewness	0.075	--	--	0.012 SE=0.011 p=0.260	0.062
Coronal	FEV1:FVC	Kurtosis	0.06	--	--	0.001 SE=0.001 p=0.539	0.056
Coronal	FEV1:FVC	FractalD	0.025	1.248 SE=0.285 p<0.001	0.295 SE=0.364 p=0.419	--	0.161
Coronal	FEV1:FVC	Moran's I	0.225	--	--	-0.716 SE=0.181 p<0.001	0.148
Coronal	FEV1:FVC	Geary's C	<0.001	1.506 SE=0.314 p<0.001	-0.513 SE=0.397 p=0.198	--	0.195
Sagittal	FEV1	Skewness	0.007	0.675 SE=0.111 p<0.001	0.214 SE=0.137 p=0.122	--	0.591
Sagittal	FEV1	Kurtosis	0.004	0.072 SE=0.013 p<0.001	0.021 SE=0.013 p=0.119	--	0.58

Sagittal	FEV1	FractalD	<0.001	10.081 SE=1.903 p<0.001	0.806 SE=2.246 p=0.720	--	0.572
Sagittal	FEV1	Moran's I	<0.001	-7.054 SE=1.891 p<0.001	4.403 SE=2.463 p=0.076	--	0.539
Sagittal	FEV1	Geary's C	<0.001	10.629 SE=2.216 p<0.001	-0.481 SE=2.015 p=0.812	--	0.554
Sagittal	FVC	Skewness	0.036	0.757 SE=0.136 p<0.001	0.320 SE=0.169 p=0.060	--	0.62
Sagittal	FVC	Kurtosis	0.037	0.078 SE=0.016 p<0.001	0.033 SE=0.016 p=0.043	--	0.608
Sagittal	FVC	FractalD	0.017	8.980 SE=2.414 p<0.001	1.149 SE=2.849 p=0.687	--	0.575
Sagittal	FVC	Moran's I	0.001	-5.213 SE=2.342 p=0.028	6.842 SE=3.051 p=0.026	--	0.564
Sagittal	FVC	Geary's C	0.05	8.425 SE=2.806 p=0.003	1.258 SE=2.551 p=0.623	--	0.559
Sagittal	FEV1:FVC	Skewness	0.056	--	--	0.014 SE=0.012 p=0.227	0.063
Sagittal	FEV1:FVC	Kurtosis	0.02	0.004 SE=0.002 p=0.022	-0.001 SE=0.002 p=0.388	--	0.089
Sagittal	FEV1:FVC	FractalD	0.003	1.006 SE=0.227 p<0.001	0.070 SE=0.268 p=0.796	--	0.168
Sagittal	FEV1:FVC	Moran's I	0.014	-1.056 SE=0.216 p<0.001	-0.206 SE=0.281 p=0.466	--	0.186
Sagittal	FEV1:FVC	Geary's C	<0.001	1.305 SE=0.252 p<0.001	-0.378 SE=0.229 p=0.101	--	0.221

LEGENDS FOR ILLUSTRATIONS

Figure E1. Mean radiomic features throughout the lung for sarcoidosis and healthy controls. Shaded bars represent 95% confidence bands; individual lines represent raw radiomic features throughout the lung per individual, colored by disease group. Results are shown for the right lung and all orientations.

Figure E2. Effect size of the absolute difference in radiomic features throughout the lung between sarcoidosis and healthy control subjects, adjusted for gender, age, and BMI. Assuming a normal approximation, values above 1.96 represent statistically significant differences at a significance level of 0.05. Results are shown for the right lung.