Computed Tomographic Phenotypes in Pulmonary Sarcoidosis — *Results of a Multinational Delphi Study*

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SUMMARY

Background

In contrast with computed tomographic (CT) appearances, histopathological findings— and, specifically, non-caseating granulomas — do not explain the major variability in clinical features, physiology and outcome in pulmonary sarcoidosis. We aimed to establish, by multinational consensus, agreement on CT/morphological phenotypes in sarcoidosis.

Methods

Thematic interviews with Core Expert Panel members (chest physicians, n=6 and thoracic radiologists, n=6; all with established research experience in sarcoidosis and/or interstitial lung diseases), yielded 34 Delphi statements, focused on the spectrum of possible CT phenotypes but included relationships between specific CT features, lung function tests, clinical features and outcome. Delphi participants were members of the i) Core Expert Panel, ii) Fleischner Society (FS) and/or The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), and iii) the nominees (maximum, n=3), of FS and WASOG members. In two Delphi rounds participants responded employing a standard 5-point Likert scale (strongly agree, agree, neutral/unsure, disagree and strongly disagree); an *a priori* threshold of ≥70% agreement (strongly agree or agree) or ≥70% disagreement (strongly disagree or disagree) was considered consensus. Statements with >30% but <70% agreement in Round 1 were amended as necessary for clarity and entered in Round 2 whereas statements with ≤30% agreement in Round 1 were excluded thereafter.

Findings

Of 174 invitees, 146 (84%; M=82. Physicians, n=98, radiologists, n=48; mean duration in practice, 21±10 years), originating from 28 countries (UK/Europe=39%; USA=25%), completed the Delphi. After Round 1, 13/34 (38%) statements reached ≥70% consensus agreement (including a statement on the utility of 'baseline' CT in patients with evidence of interstitial disease: 138/146 [94%]) and ≥70% consensus disagreement on 3/34 (9%). There was unequivocal agreement on the statements that i) there are distinct CT phenotypes in sarcoidosis (142/146 [97%]) and ii) CT features are broadly categorised as fibrotic or non-fibrotic (121/146 [83%]). On completion of Round 2, consensus was reached on seven CT phenotypes categorised as non-fibrotic (nodular patterns, n=3; consolidation, n=1) and fibrotic (n=3; bronchocentric fibrosis with or without cavitation and a mimic of progressive massive fibrosis).

Interpretation

Experts overwhelmingly recommend 'baseline' CT in sarcoidosis patients with evidence of parenchymal disease and agree that there are distinct fibrotic or non-fibrotic CT phenotypes. These findings have the potential to anchor future research and stimulate the development of a new morphological classification in sarcoidosis.

INTRODUCTION

In pulmonary sarcoidosis, there is major variability in patterns of lung function impairment (including obstructive, restrictive and mixed ventilatory defects), natural history, treated course and putative microbial triggers. [1-5] This has led to the view that the label, 'sarcoidosis', is simply a catch-all for a number of different entities. However, biopsy data — the traditional means of distinguishing between entities in other interstitial lung diseases (ILDs) — have not been used to identify distinct pulmonary phenotypes in sarcoidosis: histological evaluation mostly relies on sampling of lymph nodes or small bronchoscopic specimens. The current study was undertaken to explore the concept that in pulmonary sarcoidosis, morphologic evaluation based on computed tomographic (CT) findings, might provide a more discriminatory morphologic classification as a framework for future clinical and pathogenetic research.

The use of CT has several potential advantages. Whilst pattern recognition is common to both biopsy and CT, the latter allows evaluation of the *whole* lung parenchyma. In pulmonary sarcoidosis, it is well known that the morphologic manifestations are highly variable, to a degree rarely seen in other individual ILDs [2-4,6-10]. In stark contrast with CT, the grouping or 'staging' of sarcoidosis on chest radiography, as proposed by Scadding, does not allow fine morphologic distinctions to be made. Against this, to date, formal separation of morphological phenotypes, based on CT appearances, has not been attempted. The aim of the current study was to reach consensus on the recognisable HRCT phenotypes in pulmonary sarcoidosis as a basis for the future development of a morphological classification.

METHODS

The Delphi Study Management Committee & Core Expert Panel

The study was approved by the NHS Health Research Authority (Integrated Research Application System Approval No: 276717) and structured according to proposed methodological criteria for Delphi studies. [11] For the purposes of the current study a central Delphi Study Management Committee (DSMC) was formed, comprising four members: two radiologists, a chest physician experienced in the management of interstitial lung disease and a second chest physician with specific expertise in the conduct of Delphi studies.

In the first step, the DSMC invited a 'Core Expert Panel' of 13 experts, from seven countries, to participate in the initial qualitative phase (Figure 1) and 11/13 (85%) participated. Core Expert Panel members were chosen based on i) an affiliation and established practice in an international teaching institution and ii) verifiable research contributions in sarcoidosis and/or interstitial lung diseases. The Core Expert Panel comprised chest physicians (n=5) and thoracic radiologists (n=6). The principal role of the Core Expert Panel was to develop statements for the Delphi survey. To this end, a member of the DSMC conducted individual virtual interviews (Zoom Video Communications Inc., San Jose, California) with Core Expert Panel members using open-ended questions designed to encourage experts to provide opinions on the broad discussion themes; interviews covered five broad clinical-radiological-pathological themes (Table 1).

Virtual meetings were recorded and transcribed using a commercial transcription service (Rev.com, Austin, Texas). Meeting transcripts were subsequently reviewed and condensed into key concepts using a 'content analysis' approach, with interviews continued until theme saturation was achieved. [12] Delphi statements were constructed from core panel interviews. Delphi statements for Round 1 were created using concepts/themes

raised at interview and the clinical/radiological experience of the DSMC. For example, the theme 'PMF phenotype, even with airway distortion, can respond dramatically to treatment' gave rise to the following Delphi statement: '*A HRCT pattern comprising large mid/upper zone-predominant bronchocentric masses (i.e. progressive massive fibrosis [PMF] look-alike) can regress with treatment*'.

Selection of 'Nominators' & 'Nominees' for the Sarcoidosis Delphi Study

Following the thematic interviews, a system was devised to facilitate the recruitment of international experts. The system comprised a 'Nominating Panel' and 'Nominees'. Nominators were invited members of The Fleischner Society and/or The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) with a proven expertise and track-record of peer-reviewed publications in sarcoidosis and/or interstitial lung disease. Members of the Nominating Panel were invited both to participate in the Delphi process and to nominate up to three nominees (physicians or radiologists), with experience in sarcoidosis, with efforts made to achieve geographical and gender representation. The final list of Delphi participants comprised members of i) the Core Expert Panel, ii) the Nominating panel and iii) the Nominees.

The Delphi Survey

Delphi statements were presented to participants using commercial survey software (Qualtrics; Qualtrics XM, Seattle, Washington), a web-based survey tool that provides a user-interface for data collection. For each Delphi statement, observers were required to indicate a level of agreement, using a 5-point Likert scale as follows: strongly agree, agree,

neutral / unsure, disagree and strongly disagree. Participants were also encouraged to add free-text comments for each statement, including any proposed changes, clarifications and/or potential new questions for the subsequent round. For the majority of Delphi statements regarding HRCT appearances, anonymised full volumetric 'sample' HRCT datasets were provided as visual examples. All participants were sent individualised links to the survey by email via the Qualtrics platform, with the request to complete the survey in ≤4 weeks with weekly reminders from the DSMC.

Statistical Methods – 'Consensus Opinion' in Delphi Studies

The definition of what constitutes *consensus* in a Delphi survey varies. [13] For the current study, an *a priori* threshold of ≥70% agreement (strongly agree or agree) was used on the basis that a large number of participants were to be included which would likely result in an inherently lower standard deviation of responses. Similarly ≥70% disagreement (strongly disagree or disagree) was considered to have met consensus. Statements with ≤30% agreement in Round 1 were defined as '*unlikely to reach consensus*' and excluded from Round 2.

Outlining the criteria for termination of a Delphi study is also an important study quality metric. [11] Accordingly, from the outset, we determined a defined number of rounds as the most appropriate stopping criteria for the proposed Delphi study. A two-round methodology was chosen and composed as follows:

- **ROUND 1:**
  - — Consideration of all initial Delphi statements

- **ROUND 2:**
  - — Clarification of issues / questions raised in Round 1 (with provision of results from Round 1 where relevant)
  - — Refining questions based on participant comments

— Addition of further Delphi statements, where relevant

A ‘two-round’ method was judged ideal to allow initial statements to be refined based on results and participant feedback. Additional rounds were considered unlikely to yield greater consensus and risked increasing participant attrition [14] and furthermore, the clinical utility of any established phenotypes would require validation with formal research rather than expert opinion.

RESULTS

Core Expert Panel Interviews

Twenty-two concepts or themes emerged from the interviews conducted with Core Expert Panel members and centred broadly on the range of possible HRCT phenotypes, the relationships between specific HRCT features, lung function tests, clinical features, plus outcomes in sarcoidosis (Table 2). Ten concepts based on HRCT appearances were described in over 90% of thematic Core Expert Panel Interviews. Among these, there was unanimous agreement that there are distinct HRCT phenotypes in sarcoidosis but diverse views on what constituted a distinct HRCT phenotype. For instance, while there was consensus that a peri-lymphatic nodular pattern represents a distinct HRCT phenotype, the suggestion of a HRCT pattern mimicking usual interstitial pneumonia was recognised by only a few Core Panel Members.

Delphi Participant Demographics & Characteristics

Of the invited participants, 146/174 (84%; radiologists, n=48 and chest physicians, n=98; mean duration in practice, 21±10 years; M:F, 82:62) completed Delphi Round 1 (Table 3). There was diverse geographical representation, but with most participants practicing in USA (25%) and UK/mainland Europe (France [10%]; Italy [9%]; UK [8%]; Netherlands [7%] and Germany [5%]) (Table 4). At registration, all but one participant (145/146 [99%]) confirmed expertise in interstitial lung disease with (130/146 [89%]) also indicating a specialist interest in sarcoidosis. The majority of radiologists (44/48 [92%]) indicated that >50% of reporting time was spent reviewing thoracic imaging studies. The number of patients with sarcoidosis assessed annually by chest physicians was distributed evenly between all categories (<50 patients through to >250 patients).

Delphi Survey Results - Agreement vs. Disagreement on Delphi Statements in Round 1 & Clarifications/Amendments for Round 2

In Round 1, 34 Delphi statements were presented. A detailed summary of responses for all Round 1 statements is provided in Table 5. At the completion of Round 1, 13/34 (38%) statements reached the agreement threshold of 70%, with no statements meeting the criteria for consensus disagreement. Three statements demonstrated <30% agreement thereby meeting the criteria for '*unlikely to reach consensus*' and were removed for the purposes of Round 2. A single statement not meeting either of these criteria ('soft' intra-thoracic nodal calcification with hepatic and splenic calcified granulomas favours histoplasmosis over sarcoidosis') was removed following a review by the DSMC as it was felt to be outside the scope of the present study.

In addition to responses to specific Delphi statements, participants also submitted 619 free-text comments; all comments were reviewed by the DSMC to identify areas of uncertainty requiring clarification in Round 2. Two key areas of uncertainty emerging from Round 1 free-text comments were i) a perception among some participants that Delphi statements were referring to the *diagnostic* utility of specified patterns/phenotypes on HRCT. Secondly, there was misinterpretation among some participants that the purpose of the study was to comment on whether the provided volumetric 'sample' HRCT datasets were representative of specific Delphi statements. Issues raised in free-text comments were resolved prior to the commencement of Round 2. Other areas of uncertainty highlighted by free-text comments were clarified by email and/or in the instructions provided for Round 2.

Finally, a single new statement '*HRCT findings strongly indicative of fibrotic disease is associated with BAL neutrophilia*', was added as a variant of an existing statement to address a topic that the DSMC felt important to explore. Thus, in Round 2, participants were

presented with 18 statements (Table 6), evaluated in the same manner as in Round 1. Importantly, in Round 2 participants were provided with feedback for all statements that had been modified after Round 1.

At the completion of Round 2, there was consensus agreement on a further 9 statements. There were no statements meeting criteria for consensus disagreement or '*unlikely to reach consensus*'.

Agreement vs. Disagreement on Delphi Statements Regarding the Role of HRCT & the Occurrence / Pathological 'Meaning' of HRCT Patterns in Sarcoidosis

On completion of Round 2, 22/35 (63%) Delphi statements presented over both Rounds reached consensus agreement. There was a high level of agreement among participants for the statement that '*HRCT should be performed at baseline in patients with sarcoidosis and evidence of pulmonary interstitial involvement*' and that '*There are distinct HRCT phenotypes in sarcoidosis*' (95% and 97% agreement respectively).

The following Delphi statements regarding the possible pathological 'meaning' of HRCT patterns also achieved consensus agreement: i) '*HRCT features can be categorised as fibrotic and non-fibrotic*' (83% agreement), ii) '*Nodules alone or a predominance of nodules are almost always non-fibrotic*' (82% agreement), and, after clarification/feedback in Round 2, iii) 'Reticulation on HRCT almost always represents fibrosis (80%), iv) Large bronchocentric masses with or without cystic/bullous destruction almost always represents fibrosis (83% agreement), v) *'(In patients with a confirmed diagnosis of sarcoidosis) a predominant ground-glass opacification pattern is almost always non-fibrotic in the absence of ancillary CT features of fibrosis'* (80% agreement). By contrast, the following Delphi statements did not reach consensus agreement: a) In patients with a confirmed diagnosis of sarcoidosis a predominant consolidation pattern is almost always non-fibrotic (33%

agreement) and b) In patients with a confirmed diagnosis of sarcoidosis a mosaic attenuation pattern is almost always non-fibrotic (56% agreement).

Agreement vs. Disagreements on Delphi Statements Regarding Distinct (Recognisable) HRCT Phenotypes in Sarcoidosis

On completion of Round 2, there was consensus agreement on seven HRCT phenotypes broadly divided into the 'non-fibrotic' and 'fibrotic' subtypes (Table 7, Figures 2 and 3). Of the agreed seven phenotypes, five reached consensus in Round 1 (consensus agreement, 78-97%). Of the non-fibrotic HRCT phenotypes, a pattern of 'Multiple peri-bronchovascular, peri-fissural / subpleural micronodules' phenotype had the highest level of expert agreement (97%). Only two phenotypes met the criteria for '*unlikely to reach consensus*' (Table 5).

Agreement vs. Disagreement on Delphi Statements Regarding the Relationships Between HRCT Phenotypes & Lung Function / Outcome

There was agreement that 'specific' HRCT appearances correspond to specific lung functional profiles: in particular, 71% agreed that a predominant reticular pattern on HRCT is associated with a restrictive lung function defect and 72% agreed that a bronchocentric pattern of fibrosis is associated with an obstructive lung function defect. In terms of relationship to outcome, most experts (72%) agreed that a minority of patients with a 'progressive massive fibrosis' pattern on HRCT partially or completely regress with treatment. Finally, lobar volume loss was considered, by consensus, a marker of poor outcome.

DISCUSSION

The principal aim of this study — we believe, the first and largest of its type — was to evaluate consensus on recognisable CT phenotypes in sarcoidosis using modified Delphi methodology. The study was undertaken as a prelude to proposing a *morphological* classification based on HRCT appearances, as opposed to the historical approach in which a wide range of morphologies are 'lumped' under the generic label of sarcoidosis. This historical approach runs counter to other diffuse diseases where 'splitting', variably based on pathological features, CT appearances, patterns of functional impairment and disease 'behaviour' or outcome is the norm [15-17]. The provision of a morphological framework for future research and as a substitute for histologic evaluation, a CT phenotype classification has attractions, by offering the potential to ground future research initiatives. In principle, this might apply to further studies on the diagnostic accuracy of individual HRCT phenotypes, patterns of pulmonary function impairment, major separations in outcome, and linkage to genetic predilection and specific sarcoidosis triggers.

A *clinical* message arising from the Delphi exercise was the strong agreement that CT should be performed at baseline in patients with evidence of pulmonary involvement. The strength of consensus was surprising: there is little doubt that CT is more sensitive than plain chest radiography (CXR) [18,19] but, to date, there has been no consensus or guidance on the role of HRCT in *routine* assessment. In the original 1999 American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disease Consensus Statement on Sarcoidosis [20], CXR was regarded the mainstay of radiological diagnosis, with CT reserved for 'atypical' findings on CXR, the detection of complications and/or the assessment of CXR-occult disease. The more recent British Thoracic Society clinical statement also suggests that the use of CT should be based

on conclusions reached by CXR evaluation. [21] Against this, a very large majority of multinational expert opinion in the present study supports the routine role of CT in evaluating the lungs at baseline, a potentially important consideration for future guideline development, though not forgetting important issues of cost, availability (and accessibility) to CT worldwide to say nothing of the added radiation burden.

In the present study, participants agreed not only that there are recognisable CT phenotypes in sarcoidosis but also that CT abnormalities may broadly be categorised as fibrotic or non-fibrotic. Among the CT phenotypic subtypes recognised by Delphi participants, there was widespread agreement about nodular patterns and, in particular, the micronodular forms. Accordingly, in the first Delphi round, 97% of participants either agreed or strongly agreed that multiple bronchocentric, peri-fissural or subpleural micronodules comprised a distinct CT pattern in sarcoidosis. This is not surprising since variants of a nodular pattern have long been regarded as 'classical' on CT in sarcoidosis. [22-28] The distinction between nodular patterns, based on size, is interesting [26,27,29] with macronodules presumably reflecting coalescence of granulomata and supposedly signifying more 'extensive' disease. [27] Taken further, and in contrast with micronodular CT patterns, Aleksoniene and co-workers reported an association between the extent of macronodules on CT and lung function decline. [26] The view that individual CT patterns might be linked to particular patterns of functional impairment is now supported by an international consensus.

Three other morphological phenotypes (namely bronchocentric reticulation with or without dense parenchymal opacification but no cavitation, bronchocentric reticulation with or without dense parenchymal opacification with cavitation and a progressive massive

fibrosis pattern) which, broadly speaking, we consider fibrotic, were identified through the Delphi process. In a previous small study comprising 80 consecutive patients with CXR stage IV disease, Abehsera et al., attempted to phenotype the different forms of fibrosis in sarcoidosis. [3] In just under half of cases, there was predominant 'central bronchial distortion': a review of the images provided by the authors suggest that this pattern corresponds to the pattern of bronchocentric reticulation without cavitation identified in our Delphi. It is noteworthy, that there was disagreement between two observers for distinguishing between the bronchial distortion and linear patterns in one of the provided images. [3] A final, but important, critique of the earlier paper would be regarding the pattern of peripheral honeycombing in sarcoidosis. A pattern mimicking UIP has been reported in sarcoidosis. [8,30,31] Furthermore, in the paper by Abehsera et al., honeycombing, not necessarily in a classic UIP-IPF distribution, was reported in nearly one third of patients. [3] In the present Delphi there was no consensus either for or against "UIP" as a distinct CT phenotype in patients with a confirmed diagnosis of sarcoidosis.

A number of morphological phenotypes not achieving consensus in Round 1 did so in the second round only after clarification. This is an obvious strength of the Delphi process which allows for clarifications between rounds. Indeed, a pattern of consolidation in patients with proven sarcoidosis eventually emerged as one of the final seven recognised CT sarcoid phenotypes. Against this, a number of proposed CT phenotypes did not achieve consensus. Indeed, the presence of scattered large cavitating nodules, a mosaic attenuation pattern and interlobular septal thickening all fell below the *a priori* threshold for consensus agreement in Delphi Round 1. There is a traditional view that the CT manifestations of sarcoidosis are highly varied. Even so, cavitating nodules (NB to be differentiated from the

fibro-cavitary disease apparent in some patients) must be considered among the rare, if not rarest, of CT manifestations. The international consensus in this study, is in line with this. By contrast, with cavitating nodules, the finding that a mosaic attenuation pattern — reflecting obstructive small airways disease — did not reach consensus was a little more surprising. Involvement of airways in sarcoidosis is well documented [2,32-35]: Gleeson and colleagues found evidence of air trapping on expiratory CT in three patients with sarcoidosis [32]. Similarly, but In a larger CT study, areas of decreased attenuation at end-expiration were present in 40/45 (89%) cases and the extent of decreased attenuation was independently linked with airflow limitation [2]. The reasons why this pattern of abnormality on CT (and, for that matter, interlobular septal thickening) did not reach consensus are not entirely clear. One explanation might be that such patterns are often seen in combination with other signs of sarcoidosis (e.g. nodules, reticulation) and, accordingly, might not be regarded as 'typical' of sarcoidosis.

The Delphi exercise also took the opportunity to explore views on possible relationships between CT appearances and i) their pathological meaning, ii) patterns of functional impairment, iii) treatment implications and iv) prognosis. With regard to the first, there was agreement that two HRCT patterns were generally indicative of established fibrosis namely, a reticular pattern and large bronchocentric masses. There seems little that is controversial or unexpected in this finding. There was also consensus on the statements that specific CT appearances correspond with specific lung function profiles, that predominant reticulation is linked with restrictive lung function indices but that bronchocentric fibrosis predicts obstructive lung function. Finally, there was consensus agreement that in a *minority* of patients, a progressive massive fibrosis (PMF)-look-alike pattern may partially or completely regress on treatment. Historically, this pattern of

fibrosis has most often been linked to occupational exposures and, more often than not, signifies 'end-stage' disease [36,37]. However, we hypothesise that a PMF-like appearance on CT may sometimes represent, at least in part, intense granulomatous aggregation.

A significant limitation in the study is that despite the multinational nature of participants, the higher representation of Western nations may have created bias, given that sarcoidosis manifestations might vary between countries and ethnicities. It is also important to emphasise that we do not consider the Delphi process to be synonymous with or a surrogate for high quality research: the clinical and pathogenetic significance of phenotypic separation requires research that goes far beyond the scope of consensus agreement. However, a formal CT classification of discrete CT phenotypes in sarcoidosis, based in part on the current study, should serve as a framework for studies of sub-group differences in genetic predilection, initiating pathways and mechanisms of progression. Historically, histologic sub-classification has served this purpose in ILDs other than pulmonary sarcoidosis. In the absence of robust categorical histologic separations between sub-groups in pulmonary sarcoidosis, CT morphologic distinctions may have a central future role.

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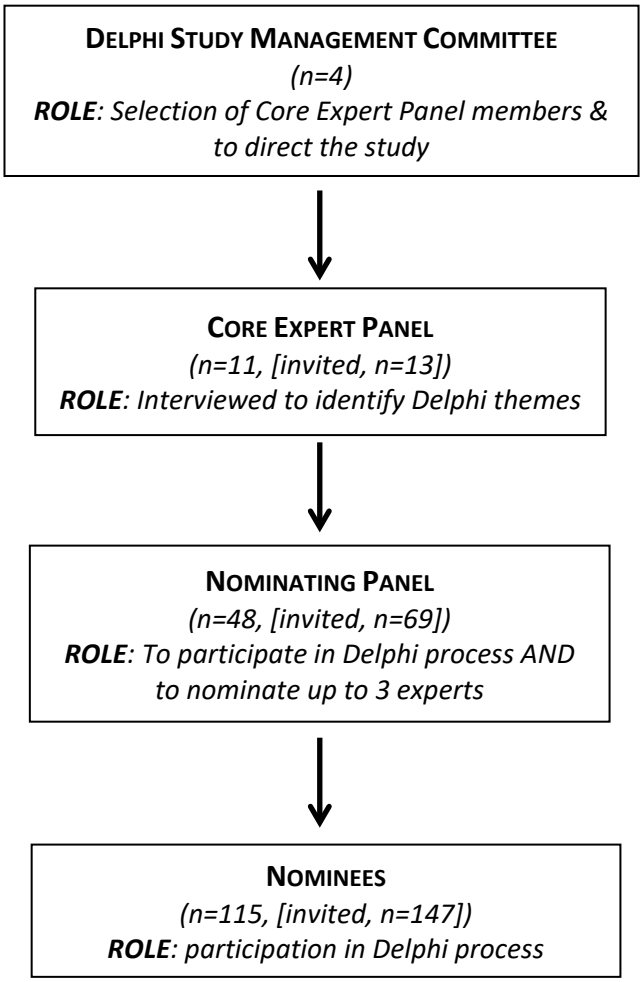

Figure 1 Composition and formation of the Delphi participants. The Delphi Study Management Committee convened the Core Expert Panel, conducted preliminary themed interviews and oversaw the Delphi process. The nominating panel (i.e. members of *The Fleischner Society* & The *World Association of Sarcoidosis and Other Granulomatous Disease* [WASOG]) participated in the Delphi process and nominated up to 3 experts in the field.

Delphi Core Expert Panel Principal Interview Themes
• Recognition of distinct HRCT appearances in sarcoidosis from own clinical practice
• Defining and categorising principal HRCT phenotypes
• Clinical / prognostic implications of HRCT phenotypes (e.g. response to treatment & survival)
• Possible relationships between HRCT phenotypes and lung function
• Potential relationships between HRCT phenotypes and bronchoalveolar lavage profiles

Table 1 Exploratory interview themes. In developing the Delphi questionnaire, all interviews followed a general theme with 'open-ended' questions posed to core panel interviewees

Concepts/themes described by >90%
▪ The CT appearances of sarcoidosis *can* be grouped into 'imaging phenotypes' ▪ A perilymphatic nodular pattern is the most frequently observed manifestation of parenchymal sarcoidosis, predicts a good prognosis and is generally responsive to treatment while fibrotic patterns confer a worse outcome. ▪ CT phenotypes in sarcoidosis can be considered *'fibrotic'* or *'non-fibrotic'*; alternatively, CT phenotypes may be *'typical'* or *'atypical'* ▪ Perihilar fibrosis with posterior retraction of the hila is a distinct fibrotic phenotype (NB described by one expert as 'pathognomonic') ▪ Perihilar reticulation is a distinct imaging feature of sarcoidosis ▪ Upper lobe fibrocavitary destruction +/- honeycombing is a recognised fibrotic phenotype ▪ Predominant ground-glass opacification (with or without nodules) indicates a non-fibrotic phenotype ▪ A CT pattern of pleuroparenchymal fibroelastosis is *not* associated with sarcoidosis ▪ A UIP pattern is a rare finding in patients with sarcoidosis (NB divided opinion over whether UIP pattern is truly a manifestation of sarcoidosis or, simply, indicative of co-existent disease) ▪ No linkage between CT phenotypes and findings in bronchoalveolar lavage fluid
Concepts described by 50-90%
▪ A 'PMF-like' appearance — comprising mid-to-upper zone mass-like consolidation – is a recognised imaging phenotype ▪ Fibrocavitary destruction with mycetoma confers a particularly poor prognosis
Concepts described by 10-50%
▪ The PMF phenotype, even with airway distortion, can respond dramatically to treatment (n=3) ▪ An obstructive lung function profile is more related to bronchocentric disease than any other form of disease (n=5) ▪ A reticular pattern is related to an obstructive lung function profile (n=2). ▪ A mosaic pattern can present in isolation and therefore may form a distinct, albeit rare, phenotype (n=2) ▪ Discrete cavitating nodules are a rare presentation of sarcoidosis (n=2)

Concepts raised by <10%
▪ 'Soft' mediastinal nodal calcification is typical of sarcoidosis; calcified granulomas in the liver and spleen favours histoplasmosis (common in USA) over sarcoidosis ▪ Diffuse interlobular septal thickening is a rare presentation of sarcoidosis (n=1) ▪ Even in advanced disease, prognosis is good and imaging appearances often remain unchanged for years (n=1) ▪ Lung volume may be an important prognostic marker: marked volume loss (esp. upper lobes) anecdotally fares worse (n=1) ▪ A lymphocytic BAL profile is most frequently seen in patients with a nodular pattern due to active disease (n=1)

Table 2 Key concepts raised by core expert panel members based on 'thematic' interviews. The themes and concepts elucidated from interviews formed the basis of Round 1 Delphi statements

Delphi Participant Characteristics (n=146)	
Specialty	
Chest Physician	98 (67.1)
Radiology	48 (32.9)
Age	53 ± 10 years
Sex (M:F)	82:62†
Years in senior practice	21 ± 10 years
Special interest in ILD/ sarcoidosis	145 (99.3)/130 (89)
RADIOLOGISTS: ***Proportion of time devoted to thoracic imaging***	
<25%	1 (2.1)
25-50%	3 (6.3)
51-75%	14 (29.2)
>75%	30 (62.5)
CHEST PHYSICIANS: ***Approximate numbers of sarcoid patients evaluated/year***	
<50	23 (23.5)
50-100	24 (24.5)
101-250	27 (27.6)
>250	24 (24.5)

Table 3 Demographic and other characteristics of participants completing the Delphi study.
Data are numbers with percentages in parenthesis. †'*Prefer not to say*' (n=2)

COUNTRY	No (%)	COUNTRY	No (%)	COUNTRY	No (%)	COUNTRY	No (%)
Argentina	4 (2.7)	**Denmark**	1 (0.7)	**Mexico**	1 (0.7)	**South Africa**	2 (1.4)
Australia	2 (1.4)	**France**	14 (9.6)	**Netherlands**	10 (6.8)	**South Korea**	8 (5.5)
Austria	1 (0.7)	**Germany**	7 (4.8)	**New Zealand**	2 (1.4)	**Spain**	5 (3.4)
Belgium	2 (1.4)	**Greece**	1 (0.7)	**Portugal**	2 (1.4)	**Switzerland**	1 (0.7)
Brazil	2 (1.4)	**India**	4 (2.7)	**Romania**	1 (0.7)	**Turkey**	2 (1.4)
Canada	2 (1.4)	**Italy**	13 (8.9)	**Russia**	4 (2.7)	**UK**	11 (7.5)
Chile	1 (0.7)	**Japan**	6 (4.1)	**Serbia**	1 (0.7)	**USA**	36 (24.7)

Table 4 Geographical distribution of participants in the Delphi study. The table shows the numbers of participants by country with percentages in parentheses. The highest proportion of participants were practicing in USA or UK/major mainland European countries

Table 5 – Round 1 Delphi Responses								
Delphi Statement Number	**Delphi Statement**	**Strongly Agree**	**Agree**	**Neutral/ Unsure**	**Disagree**	**Strongly Disagree**	**Total Agree (%)**	**Total Disagree (%)**
1	**HRCT should be performed at baseline in patients with sarcoidosis and evidence of pulmonary interstitial involvement**	107	31	4	4	0	**138 (94.5)**	**4 (2.7)**
2	**There are distinct HRCT phenotypes in sarcoidosis**	84	58	4	0	0	**142 (97.3)**	**0 (0)**
3	**HRCT features can be categorised as 'fibrotic' and 'non-fibrotic'**	29	92	16	8	1	**121 (82.9)**	**9 (6.2)**
4	**Nodules alone or a predominance of nodules are almost always non-fibrotic**	44	75	16	10	1	**119 (81.5)**	**11 (7.5)**
5	**A predominant ground-glass opacification pattern is almost always non-fibrotic**	22	57	38	28	1	**79 (54.1)**	**29 (19.9)**
6	**A predominant consolidation pattern is almost always non-fibrotic**	8	42	38	50	8	**50 (34.2)**	**58 (39.7)**
7	**A predominant mosaic attenuation pattern is almost always non-fibrotic**	17	44	38	44	3	**61 (41.8)**	**47 (32.2)**
8	**Nodules as the predominant or sole abnormality are a distinct HRCT pattern in sarcoidosis**	53	67	13	13	0	**120 (82.2)**	**13 (8.9)**
9	**Multiple peri-bronchovascular, peri-fissural / subpleural micronodules is a distinct pattern**	105	37	1	2	1	**142 (97.3)**	**3 (2.1)**
10	**Multiple *randomly* distributed micronodules is a distinct pattern**	16	67	31	28	4	**83 (56.8)**	**32 (21.9)**
11	**Multiple larger peri-bronchovascular nodules is a distinct pattern**	33	81	19	10	3	**114 (78.1)**	**13 (8.9)**
12	**Scattered larger nodules is a distinct pattern**	11	57	35	39	4	**68 (46.6)**	**43 (29.5)**

13	**Scattered larger cavitating nodules is a distinct pattern**	3	24	30	65	24	**27 (18.5)**	**89 (61)**
14	**Ground-glass opacification as the predominant or sole abnormality is a distinct pattern**	12	54	22	47	11	**66 (45.2)**	**58 (39.7)**
15	**Consolidation as the predominant or sole abnormality is a distinct pattern**	18	73	25	27	3	**91 (62.3)**	**30 (20.5)**
16	**Mosaic attenuation as the predominant or sole abnormality is a distinct pattern**	8	34	32	56	16	**42 (28.8)**	**72 (49.3)**
17	**Reticulation on HRCT almost always represents fibrosis**	20	66	28	28	4	**86 (58.9)**	**32 (21.9)**
18	**Interlobular septal thickening on HRCT represents fibrosis**	7	26	37	60	16	**33 (22.6)**	**76 (52.1)**
19	**Large bronchocentric masses with or without cystic / bullous 'destruction' on CT in sarcoid almost always represents fibrosis**	23	67	23	32	1	**90 (61.6)**	**33 (22.6)**
20	**Bronchocentric reticulation +/- dense parenchymal opacification WITHOUT cavitation is a distinct pattern**	49	69	22	6	0	**118 (80.8)**	**6 (4.1)**
21	**Bronchocentric reticulation and dense parenchymal opacification WITH cavitation is a distinct pattern**	38	76	19	12	1	**114 (78.1)**	**13 (8.9)**
22	**Large bronchocentric masses (i.e. progressive massive fibrosis [PMF] look-alike) is a distinct pattern**	43	73	21	8	1	**116 (79.5)**	**9 (6.2)**
23	**Predominant interlobular septal thickening is a distinct pattern**	9	54	35	48	0	**63 (43.2)**	**48 (32.9)**
24	**Mid/lower zone-predominant subpleural reticulation with or without honeycombing (i.e. UIP / NSIP look-alike) is a distinct pattern**	14	43	22	45	22	**57 (39)**	**67 (45.9)**
25	**PPFE look-alike is a distinct pattern**	12	55	44	30	5	**67 (45.9)**	**35 (24)**
26	**'Soft' intra-thoracic (mediastinal / hilar) nodal calcification occurs in sarcoidosis**	70	70	5	1	0	**140 (95.9)**	**1 (0.7)**

27	**'Soft' intra-thoracic nodal calcification with hepatic and splenic calcified granulomas favours histoplasmosis over sarcoidosis†**	18	47	58	21	2	**65 (44.5)**	**23 (15.8)**
28	**Specific HRCT appearances correspond to specific lung function profiles**	16	72	35	19	4	**88 (60.3)**	**23 (15.8)**
29	**A predominant reticular pattern on HRCT is associated with a restrictive lung function defect**	14	89	28	15	0	**103 (70.5)**	**15 (10.3)**
30	**A bronchocentric pattern of fibrosis is associated with an obstructive lung function defect**	11	68	45	22	0	**79 (54.1)**	**22 (15.1)**
31	**A predominant nodular pattern on HRCT is associated with a BAL lymphocytosis**	17	71	46	12	0	**88 (60.3)**	**12 (8.2)**
32	**Bronchocentric reticulation +/- dense parenchymal opacification WITH cavitation predicts a poor response to treatment**	40	80	19	6	1	**120 (82.2)**	**7 (4.8)**
33	**A PMF look-alike pattern can regress with treatment**	8	70	28	36	4	**78 (53.4)**	**40 (27.4)**
34	**Lobar volume loss (particularly the upper lobes) is associated with a poor outcome in sarcoidosis**	7	71	53	14	1	**78 (53.4)**	**15 (10.3)**

Table 5 Responses to Round 1 Delphi statements. Colour-coding indicates statements reaching consensus threshold agreement (≥70% agreement; ***in dark green***), statements with indeterminate agreement in Round 1 (≥30 to <70% agreement; ***in light green***) and statements unlikely to reach consensus (<30% agreement; ***in red***).

†Statement 27 was considered outside the scope of the study and accordingly excluded from Round 2. HRCT=high-resolution CT; PMF=progressive massive fibrosis; UIP=usual interstitial pneumonia; NSIP=non-specific interstitial pneumonia; PPFE=pleuroparenchymal fibroelastosis; BAL=bronchoalveolar lavage

Table 6 – Round 2 Delphi Responses								
Statement Number (Round 1)	**Delphi Statement**	**Strongly Agree**	**Agree**	**Neutral/ Unsure**	**Disagree**	**Strongly Disagree**	**Total Agree (%)**	**Total Disagree (%)**
	IN PATIENTS WITH A CONFIRMED DIAGNOSIS OF SARCOIDOSIS…*							
5	**A predominant ground-glass opacification pattern is almost always non-fibrotic *(in the absence of ancillary HRCT features of fibrosis)***	32	83	17	11	1	**115 (79.9)**	**12 (8.3)**
6	**A predominant consolidation pattern is almost always non-fibrotic**	9	38	29	61	7	**47 (32.6)**	**68 (47.2)**
7	**A predominant mosaic attenuation pattern is almost always non-fibrotic**	18	62	25	38	1	**80 (55.6)**	**39 (27.1)**
10	**Multiple randomly distributed micronodules is a distinct nodular phenotype**	31	64	17	26	6	**95 (66.0)**	**32 (22.2)**
12	**Scattered larger nodules is a distinct nodular phenotype**	23	82	20	14	4	**105 (72.9)**	**18 (12.5)**
14	**Ground-glass opacification as the predominant or sole abnormality is a distinct pattern**	22	64	12	41	5	**86 (59.7)**	**46 (31.9)**
15	**Consolidation as the predominant or sole abnormality is a distinct pattern in sarcoidosis**	45	88	4	6	1	**133 (92.3)**	**7 (4.9)**
17	**Reticulation on CT almost always represents fibrosis**	33	82	9	19	1	**115 (79.9)**	**20 (13.9)**
19	**Large bronchocentric masses with or without cystic / bullous destruction almost always represents fibrosis**	50	70	11	13	0	**120 (83.3)**	**13 (9)**
23	**Predominant interlobular septal thickening is a distinct pattern**	17	83	18	21	5	**100 (69.4)**	**26 (18.1)**

24	**Mid/lower zone-predominant subpleural reticulation with or without honeycombing (i.e. UIP / NSIP look-alike) is a distinct pattern**	6	51	18	52	17	**57 (39.6)**	**69 (47.9)**
25	**PPFE look-alike is a distinct pattern**	24	76	22	19	3	**100 (69.4)**	**22 (15.3)**
28	**Specific HRCT appearances correspond to specific lung function profiles**	27	88	14	13	2	**115 (79.9)**	**15 (10.4)**
30	**A bronchocentric pattern of fibrosis is associated with an obstructive lung function defect**	24	79	28	13	0	**103 (71.5)**	**13 (9)**
31	**A predominant nodular pattern on HRCT is associated with a BAL lymphocytosis**	27	73	41	3	0	**100 (69.4)**	**3 (2)**
	HRCT findings strongly indicative of fibrotic disease is associated with BAL neutrophilia†	8	41	66	24	5	**49 (34.0)**	**29 (20.1)**
33	***A minority of patients with sarcoidosis and a*** **PMF look-alike pattern on HRCT will demonstrate partial or complete regression with treatment**	16	88	21	17	2	**104 (72.2)**	**19 (13.2)**
34	**Lobar volume loss (particularly the upper lobes) is associated with a poor outcome**	18	84	35	6	1	**102 (70.8)**	**7 (4.9)**

Table 6 Responses to Round 2 Delphi statements. Following Round 1, note that *all* statements in Round 2 were preceded with the sentence 'In patients with a confirmed diagnosis of sarcoidosis…'. Modifications made for clarity to statements in Round 1 are *underlined and italicised*.
† New statement added in Round 2 to explore a clinically important question not addressed in Round 1.

	HRCT Phenotypes
1	† Multiple peri-bronchovascular, peri-fissural / subpleural micronodules (Consensus agreement=97%; **Fig 5.3A**)
2	† Multiple larger peri-bronchovascular nodules (Consensus agreement=78%; **Fig 5.3B**)
3	†† Scattered larger nodules (Consensus agreement=73%; **Fig 5.3C**)
4	††Predominant consolidation pattern (Consensus agreement=92%; **Fig 5.3D**)
5	† Bronchocentric reticulation +/- dense parenchymal opacification *WITHOUT* cavitation (Consensus agreement=81%; **Fig 5.4A/B**)
6	† Bronchocentric reticulation +/- dense parenchymal opacification *WITH* cavitation (Consensus agreement=78%; **Fig 5.4C**)
7	† Large bronchocentric masses (PMF-look-alike) (Consensus agreement=79%; **Fig 5.4D**)

Table 7 HRCT phenotypes reaching consensus following Delphi Rounds 1 & 2. The seven principal phenotypes broadly broken down into 'non-fibrotic' (*light blue background*) and 'fibrotic' (*darker blue background*) sub-types. NB †Delphi Statements achieving consensus in Round 1; ††Delphi Statements achieving consensus in Round 2, after clarifications/feedback.

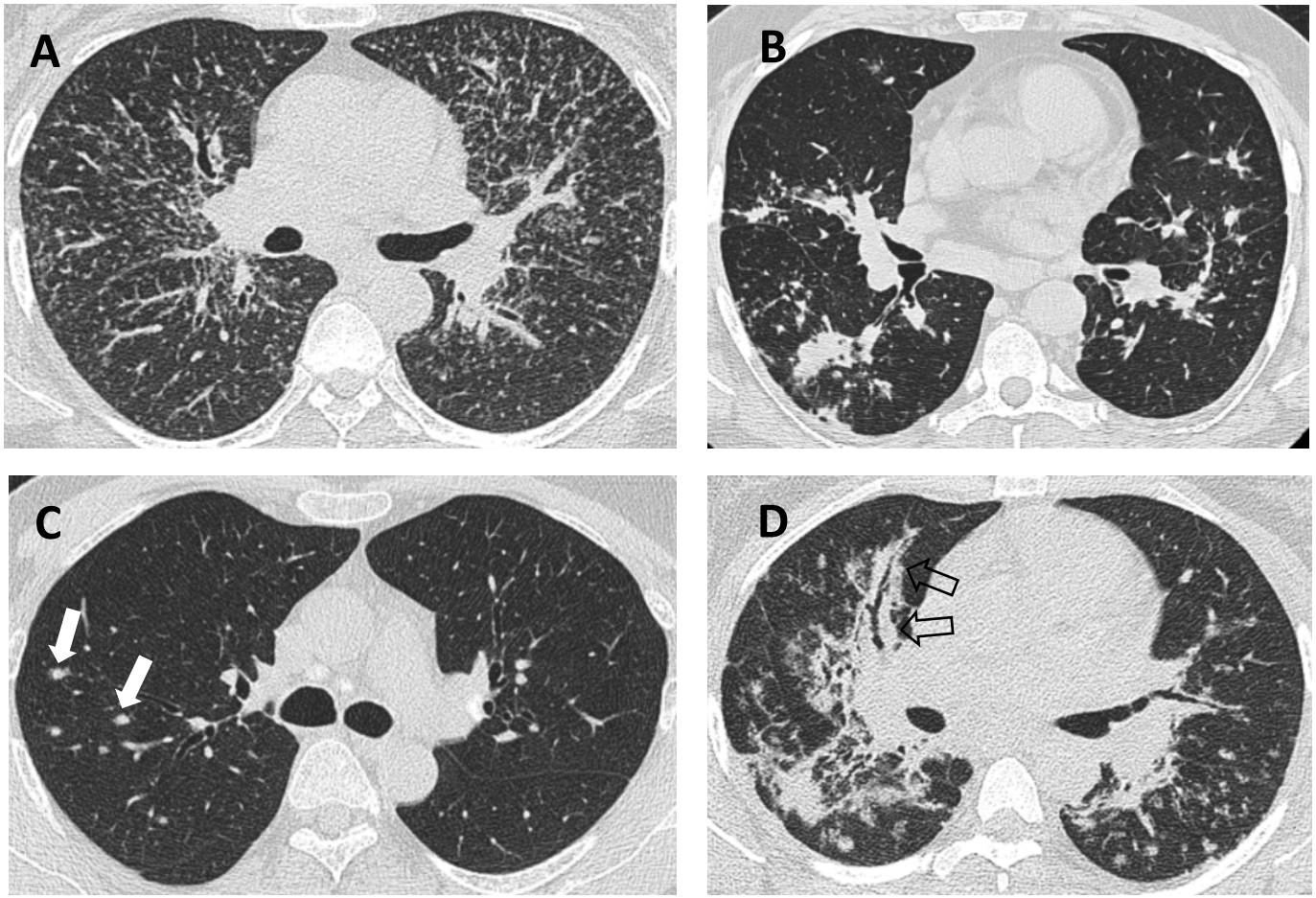

Figure 2 HRCT images showing <u>four</u> phenotypes — considered *non-fibrotic* — reaching Delphi consensus. **A)** HRCT image just below the carina showing innumerable peri-bronchovascular, peri-fissural and sub-pleural micronodules; **B)** Image in another patient with multiple larger peri-bronchovascular nodules; some of the larger nodules have smaller surrounding micronodules (the 'galaxy sign'); **C)** HRCT image at the level of the carina showing scattered larger nodules (*arrows*) which appear unrelated to bronchovascular structures and **D)** a pattern of predominant consolidation which, in the anterior segment of the right upper lobe, also appears to be strikingly bronchocentric (*open black arrows*)

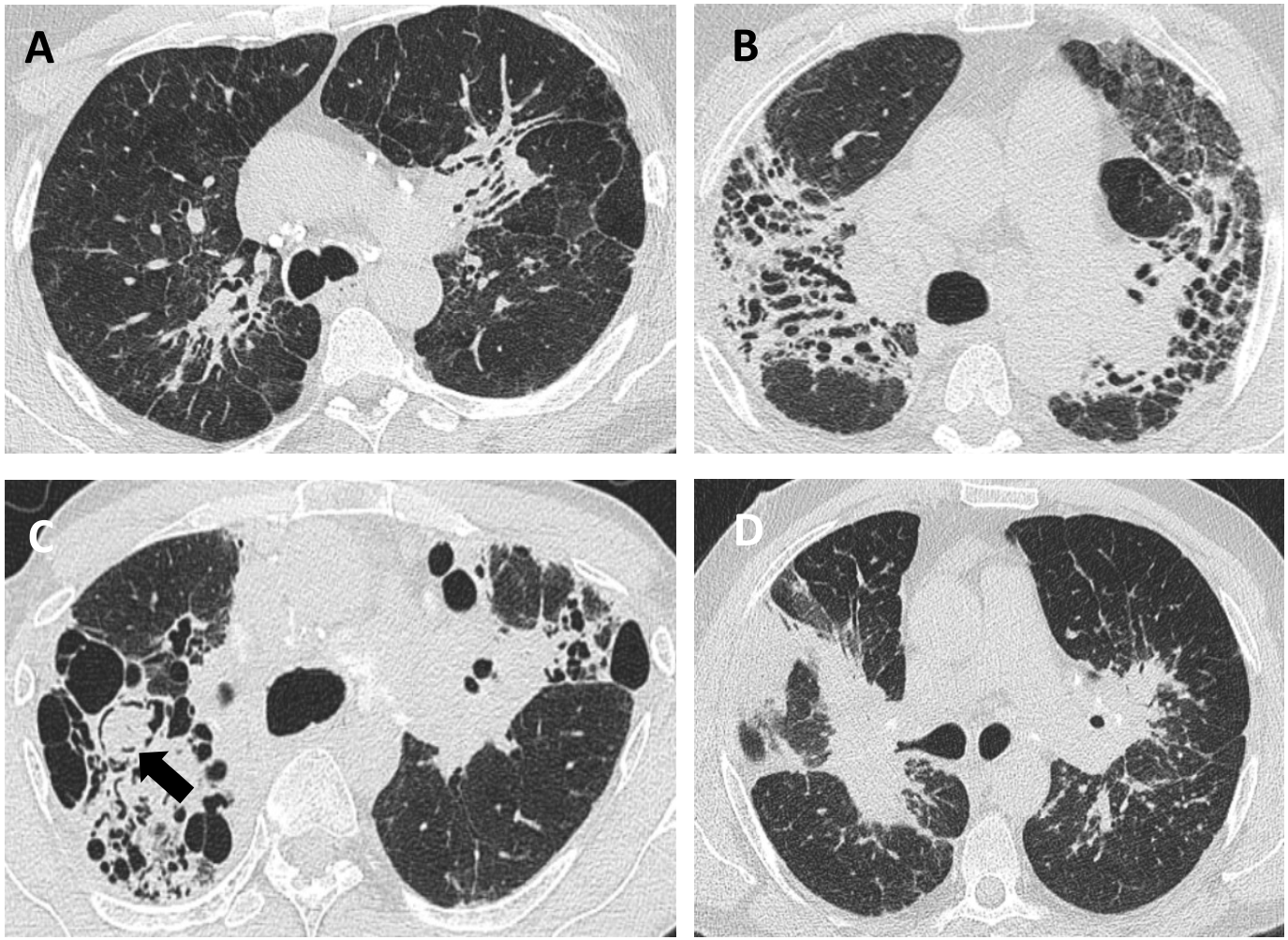

Figure 3 HRCT images showing <u>three</u> phenotypes — considered *fibrotic* — reaching Delphi consensus. **A)** HRCT image just at the carina with bilateral bronchocentric reticulation; there is also a pattern of 'loose' reticulation in both lungs; **B)** HRCT through the upper lobes, in another patient, showing more extensive, symmetrical bronchocentric reticulation; **C)** Image just above the carina demonstrating upper lobe fibrocavitary disease. NB There is a mycetoma in one of the right upper lobe cavities (*arrow*) and **D)** dense, bilateral bronchocentric 'masses' giving an appearance of progressive massive fibrosis. There are a few scattered micronodule in the left lung but this is not the dominant abnormality