CNUH
CHONNAM NATIONAL UNIVERSITY HOSPITAL

Diagnosis and Treatment of Pulmonary Sarcoidosis

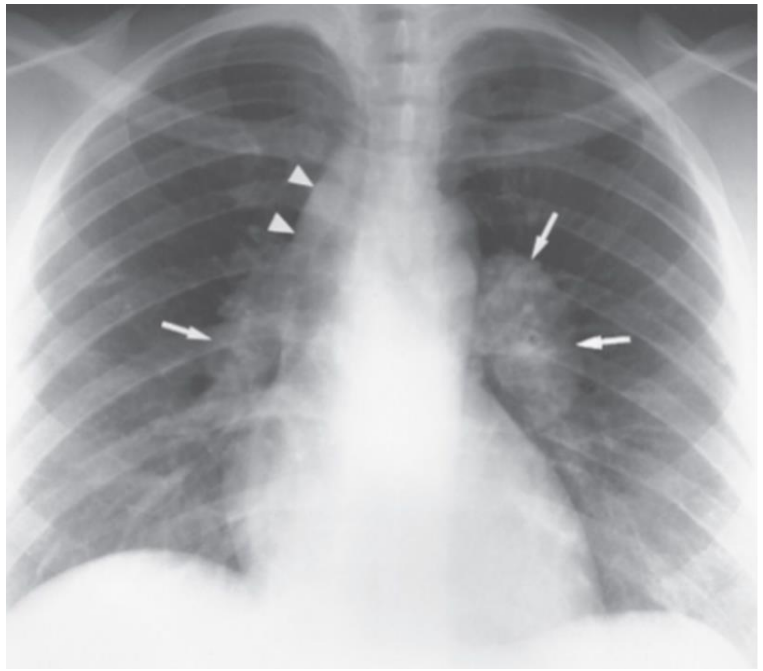
전남대학교병원 호흡기내과

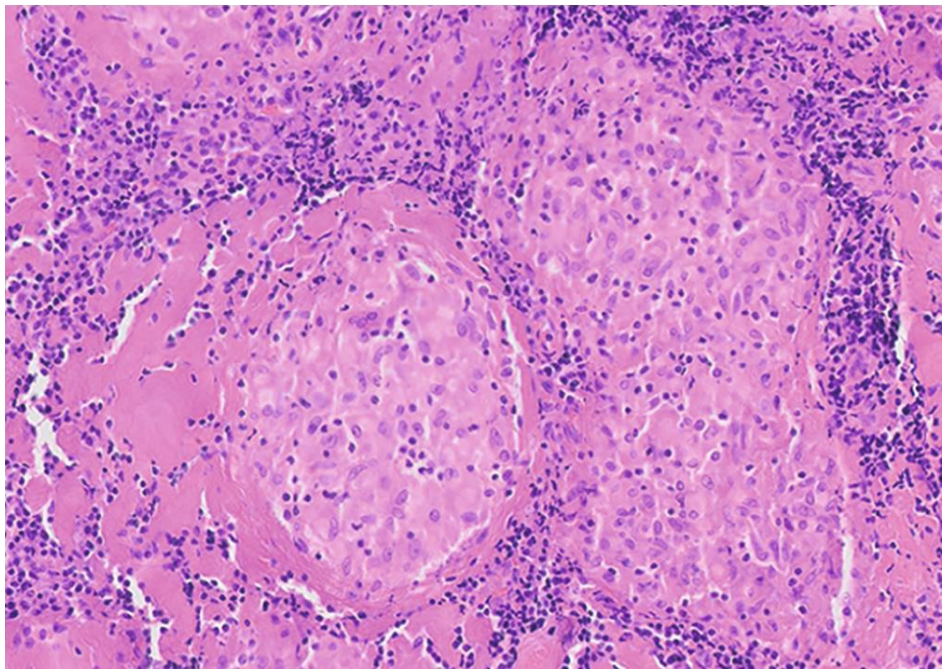
신홍준

전남대학교병원

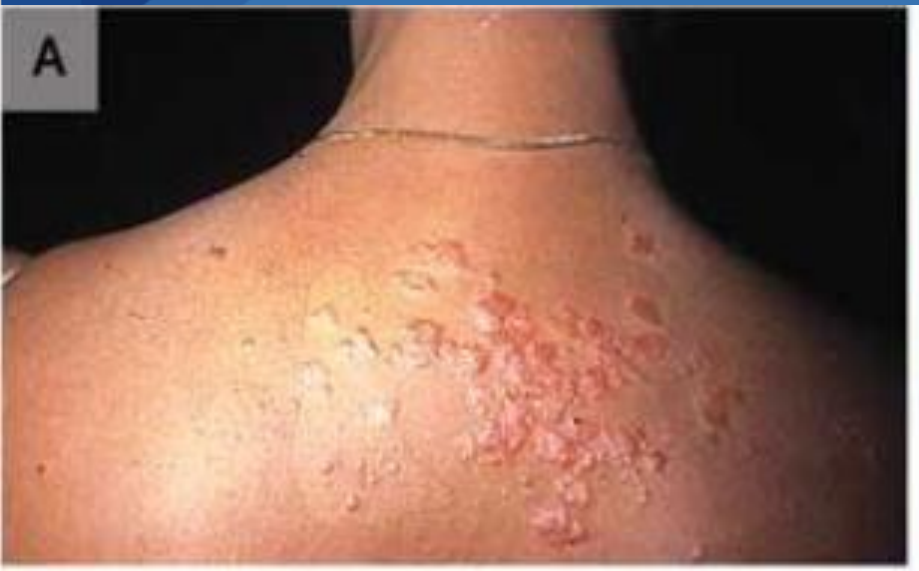
Sarcoidosis

- Sarcoidosis is an inflammatory disease characterized by the presence of non-necrotizing granulomas in virtually any organ, although the lung is the most common site.

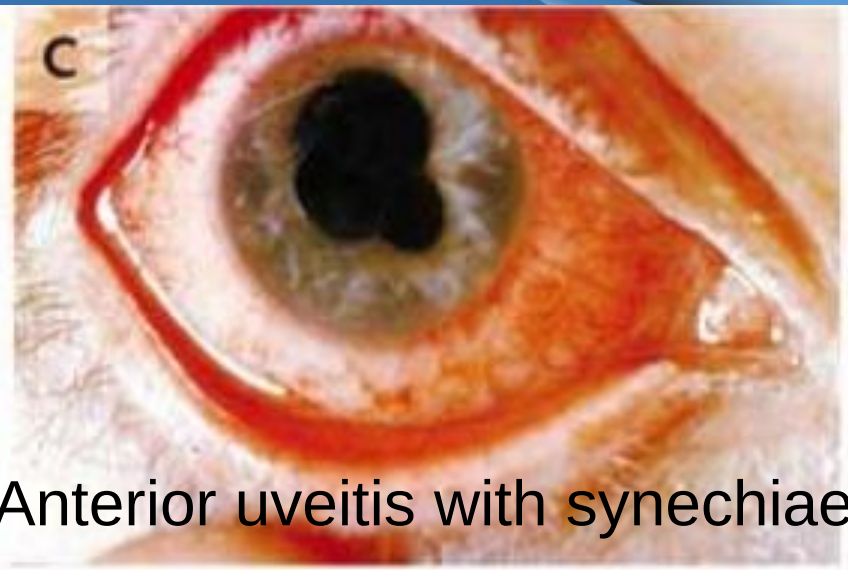




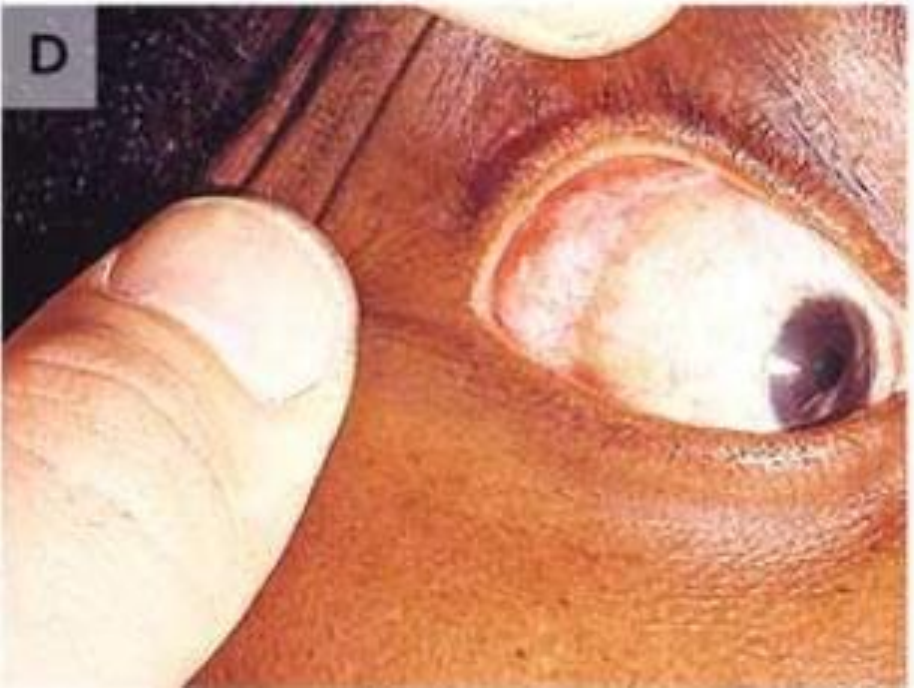
Nat Rev Dis Primers. 2019 Jul 4;5(1):45



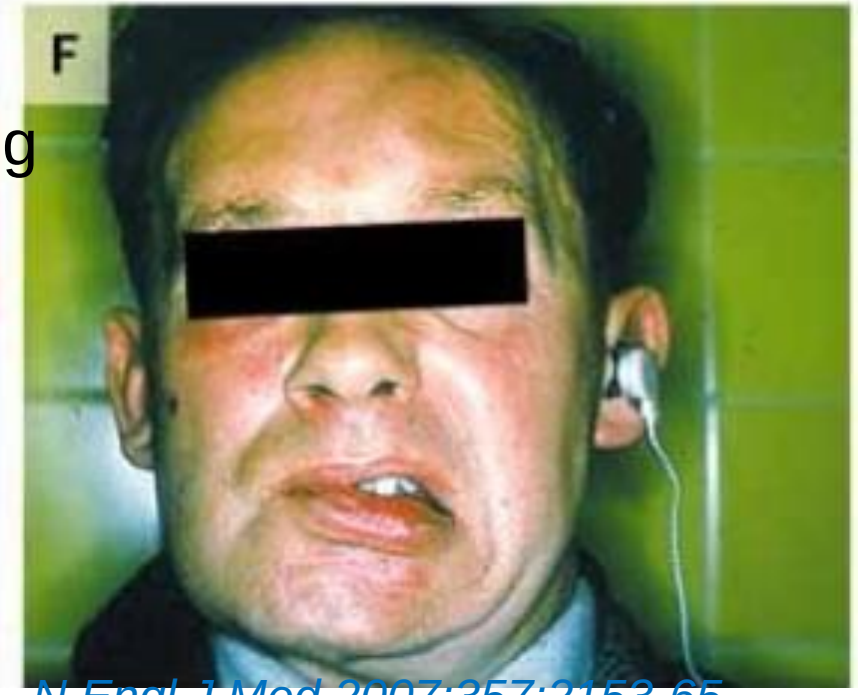
Lupus pernio



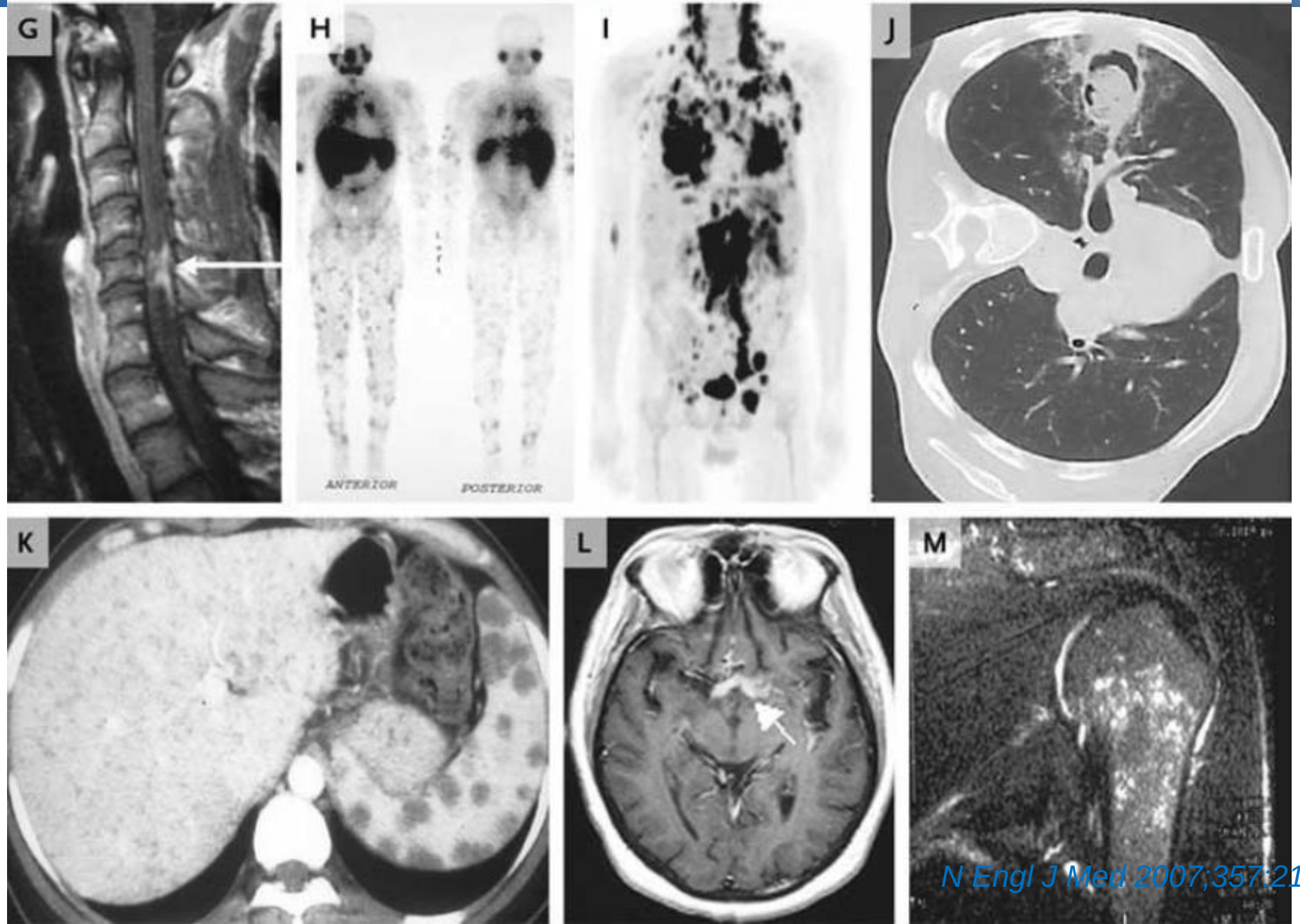
Anterior uveitis with synechiae



Endobronchial cobblestoning



N Engl J Med 2007;357:2153-65.



N Engl J Med 2007;357:2153-65.

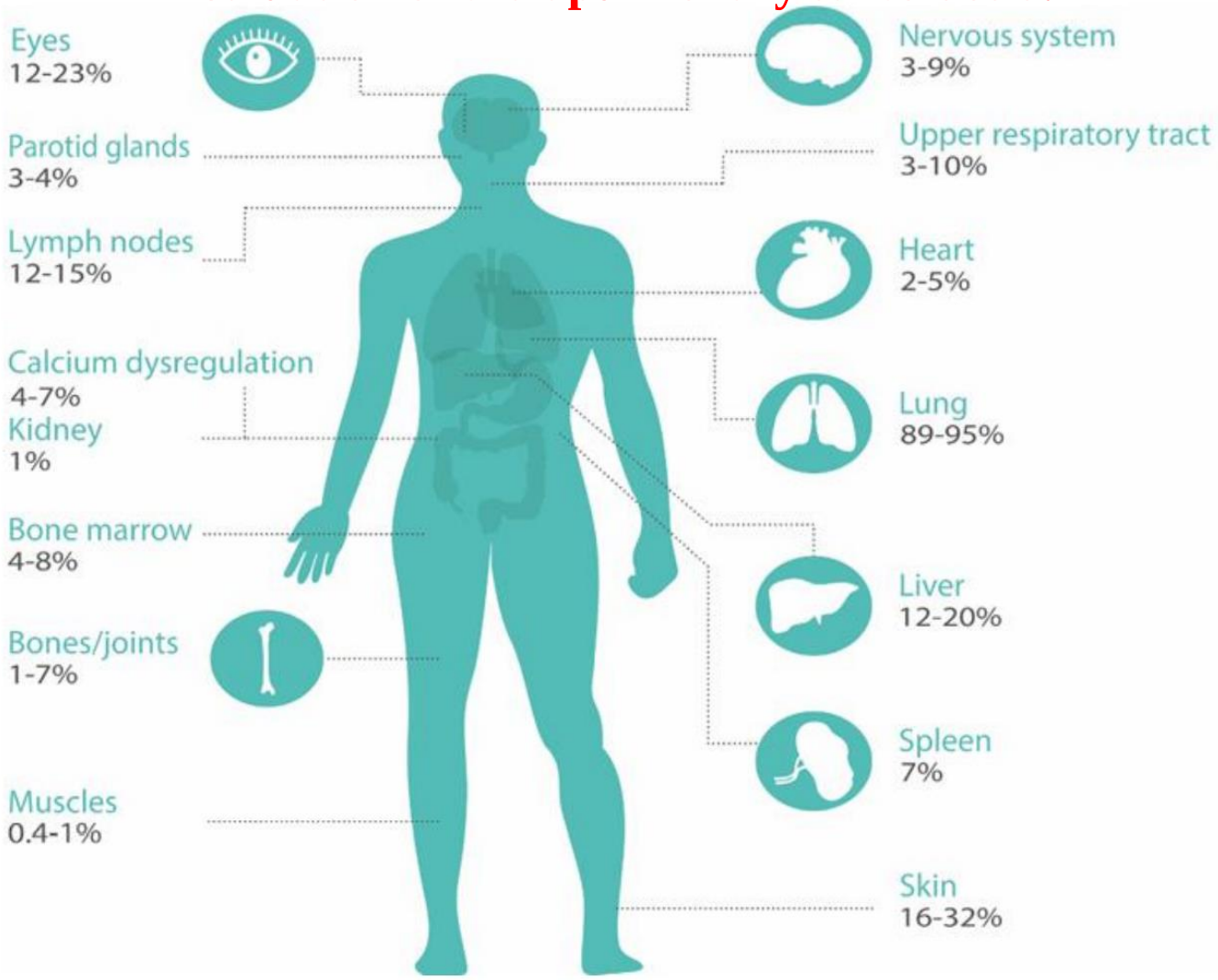
Table 3 | **Common organ involvements and symptoms in sarcoidosis**

Affected organ	Examples of related symptoms	Prevalence of organ involvement (%)[a]
Lung	Cough, dyspnoea, wheezing and stridor	89–99
Skin	Lupus pernio, papules, nodules, plaques and infiltrated scars and tattoos	16–32
Eyes	Painful and/or red eye and vision loss	5–23
Liver	Abdominal pain and elevated liver functions	12–20
Lymph nodes	Peripheral lymphadenopathy	13–15
Spleen	Abdominal pain	5–10
Nervous system	Facial palsy, fatigue (for example, pituitary insufficiency), gait disturbance, headache, hearing loss, numbness or paraesthesia, seizure, trigeminal neuralgia, vertigo, visual loss and weakness and/or paresis	3–9
Heart	Conductance disturbances, arrhythmias, dyspnoea, fatigue (for example, cardiomyopathy) and syncope	2–5

[a]Prevalence data are from REF.[280].

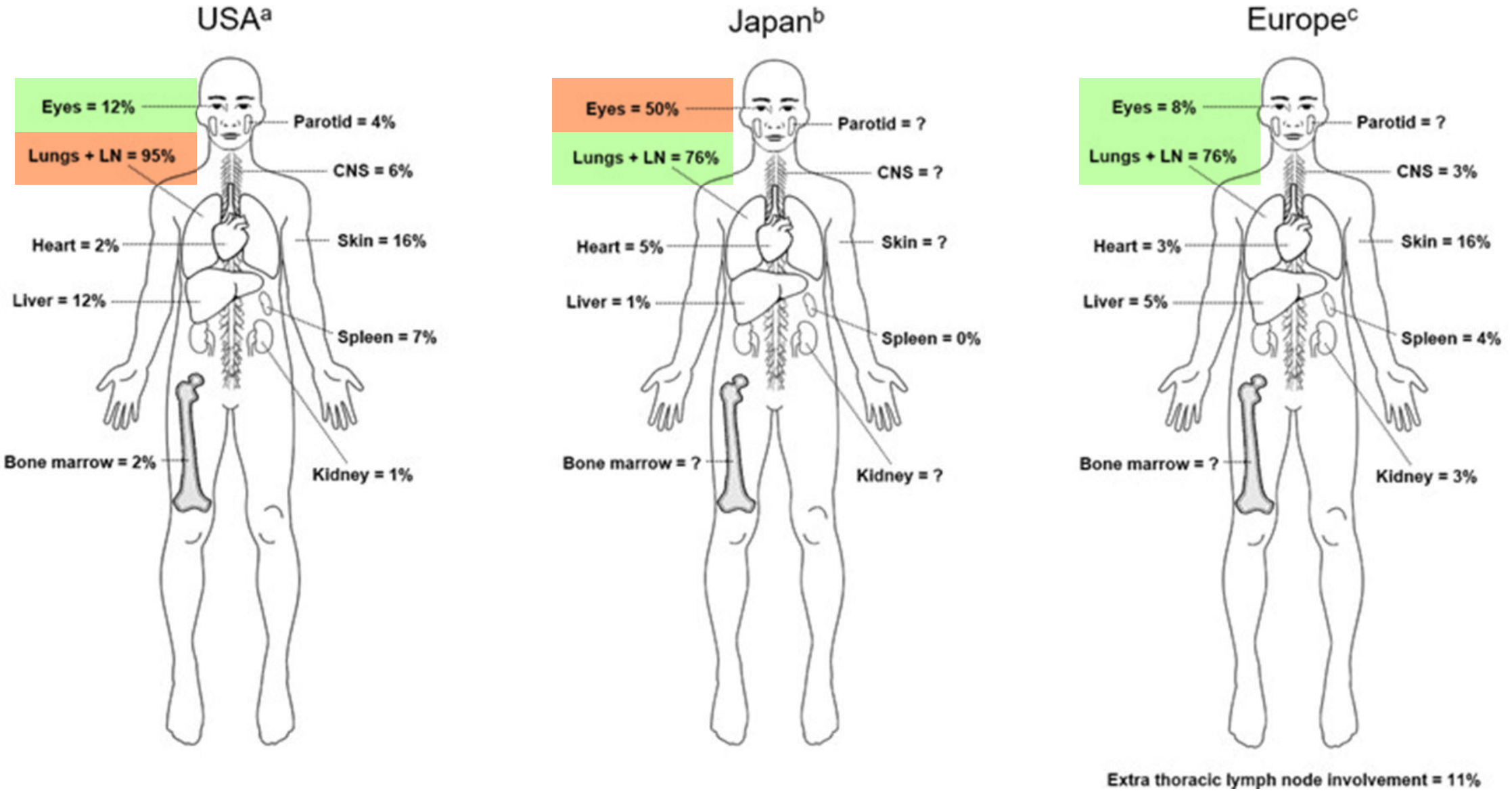
Nat Rev Dis Primers. 2019 Jul 4;5(1):45

Evaluation of extrapulmonary sarcoidosis?



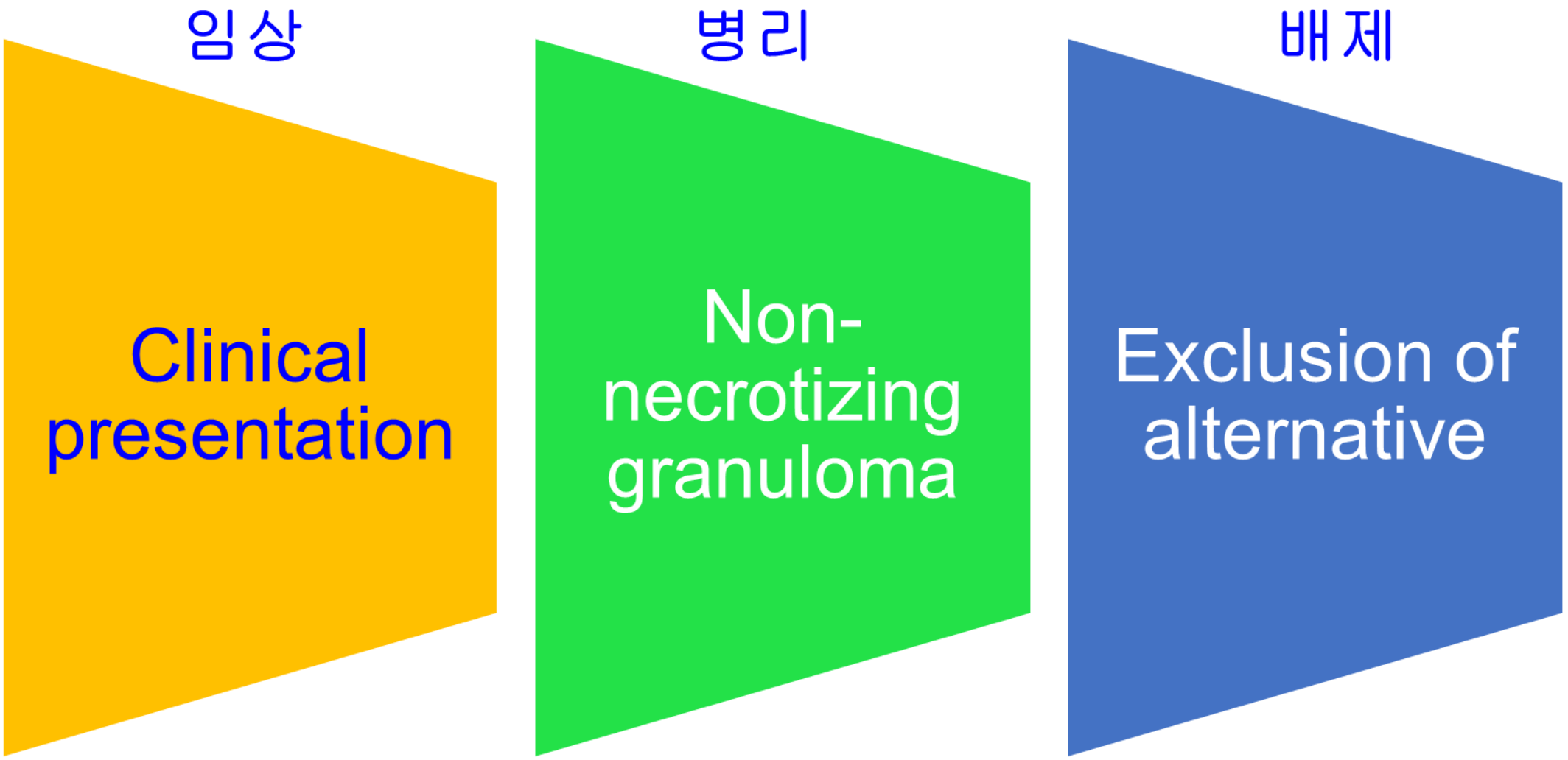
J Clin Med. 2020 Feb 1;9(2):390.

Major organ manifestations of sarcoidosis



Thorax 2021;76:4-20

Diagnosis of Sarcoidosis



Differential diagnosis	Example	Test or assessment
Bacterial infections	Mycobacterium	• Culture • Antigen or antibody detection methods
Fungal infections	Aspergillosis	• Culture • Antigen or antibody detection methods
Systemic vasculitis	Granulomatosis with polyangiitis (GPA)[a]	• Detection of ANCA • Analysis of urinary sediment • Nasal and oral assessment
IgG4-related disease	Pulmonary inflammatory pseudotumours	• Measurement of serum IgG4 level • IgG4 immunohistochemistry of biopsy samples
Exposure-induced sarcoid-like lesions	• Silicosis • Berylliosis • Hypersensitivity pneumonitis	• Extrapulmonary organ assessment (especially for silicosis; usually by FDG-PET scanning) • Assessment of birefringent crystals in silicosis (for example, in BAL fluid or lung or lymph node tissue) • BeLPT • Precipitin test in hypersensitivity pneumonitis
Drug-induced granulomas	Immunotherapy-induced granulomas	• Compatible drug exposure • Timeline with symptoms
Haematological malignancies	Lymphomas	• Cytological assessment • Histological assessment
Sarcoid-like lesions due to other diseases	• Cancer • Common variable immunodeficiency	• Cytological assessment • Histological assessment • Major organ assessment for sarcoidosis (for example, by FDG-PET scanning) • Measurement of serum immunoglobulins

Nat Rev Dis Primers. 2019 Jul 4;5(1):45

Table 2 | **Drugs or therapies that cause sarcoidosis**[a]

Agent or therapy	Examples	Type of agent or therapy
Biological response modifiers		
Cytokines	IFNα, IFNγ, IFNβ and IL-2	Recombinant protein
Immune checkpoint inhibitors	Anti-CTLA4, anti-PD1 or anti-PDL1 antibodies	Monoclonal antibody
Immune reconstitution	Bone marrow transplantation	Donor cells
Anti-retroviral therapy in patients with HIV	HAART (such as lamivudine, stavudine and indinavir or zidovudine, lamivudine and efavirenz)	Drug
Cancer chemotherapy after immune recovery	R-CHOP or paclitaxel and carboplatin or doxorubicin, cyclophosphamide and paclitaxel	Chemotherapeutic agent
Biologics		
Anti-TNF therapies	Etanercept, infliximab and adalimumab	Monoclonal antibody
BRAF inhibitors	Vemurafenib, dabrafenib and encorafenib	Small molecule

CTLA4, cytotoxic T lymphocyte antigen 4; HAART, highly active anti-retroviral therapy; PD1, programmed cell death 1; PDL1, programmed cell death 1 ligand 1; R-CHOP, combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; TNF, tumour necrosis factor. [a]Or a sarcoidosis-like drug reaction[118].

Nat Rev Dis Primers. 2019 Jul 4;5(1):45

Table 2. Clinical Evaluation in Sarcoidosis.*

Initial assessment

History and physical examination (attention to environmental or occupational exposure and family history)

Biopsy of affected organ, with special stains and culture of specimen

Posteroanterior and lateral chest radiographs

Pulmonary-function tests — spirometry with bronchodilator, total lung capacity, and diffusion capacity

Electrocardiography

Complete ophthalmologic evaluation (slit-lamp, tonometric, and funduscopic examinations)

Complete blood count with platelet count and measurement of serum calcium, creatine, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels)

Measurement of serum level of angiotensin-converting enzyme (if elevated, may be useful to monitor patient compliance)

Other tests as indicated for assessment of involved organs:

- Heart — Holter monitoring, echocardiography, cardiac PET, MRI, and electrophysiological study for inducible arrhythmias
- Lung — right-heart catheterization for pulmonary hypertension
- Central nervous system — MRI with gadolinium and cerebrospinal fluid analysis

Monitoring (follow up every 2 to 3 months)

Assessment for decline in physiological function based on initial organ involvement

Further testing in the case of new symptoms or physical findings

Testing to monitor side effects of therapy — for example, bone densitometry for corticosteroid use and semiannual ophthalmologic examination for hydroxychloroquine use

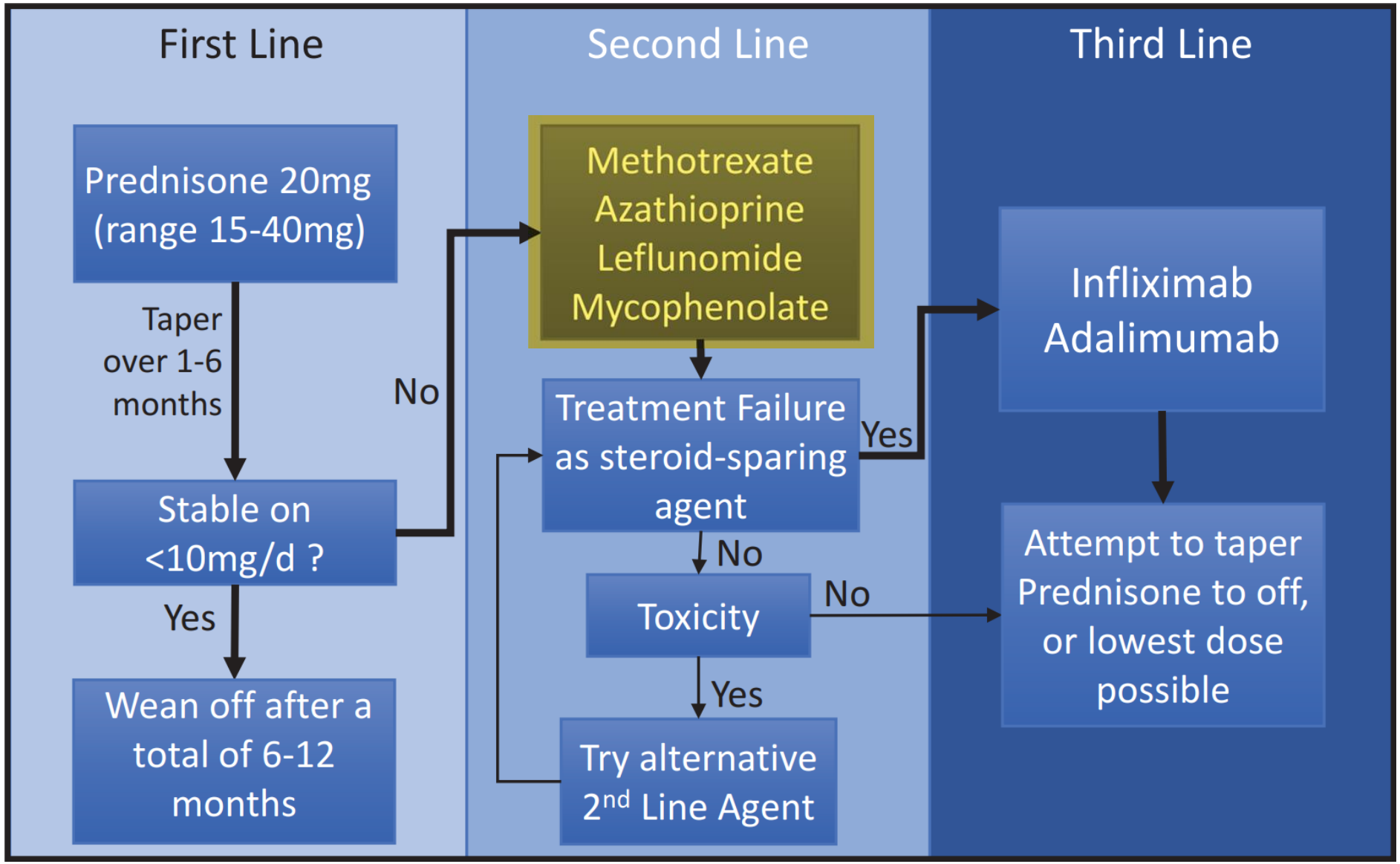
N Engl J Med 2007;357:2153-65.

Table 3. Initial Therapy According to Organ and Clinical Status.*

Organ	Clinical Findings	Treatment
Lungs	Dyspnea plus FEV_1, FVC <70%	Prednisone, 20–40 mg/day
	Cough, wheezing	Inhaled corticosteroid
Eyes	Anterior uveitis	Topical corticosteroid
	Posterior uveitis	Prednisone, 20–40 mg/day
	Optic neuritis	Prednisone, 20–40 mg/day
Skin	Lupus pernio	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day Thalidomide, 100–150 mg/day Methotrexate, 10–15 mg/wk
	Plaques, nodules	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day
	Erythema nodosum	NSAID
Central nervous system	Cranial-nerve palsies	Prednisone, 20–40 mg/day
	Intracerebral involvement	Prednisone, 40 mg per day Azathioprine, 150 mg/day Hydroxychloroquine, 400 mg/day
Heart	Complete heart block	Pacemaker†
	Ventricular fibrillation, tachycardia	AICD
	Decreased LVEF (<35%)	AICD; prednisone, 30–40 mg/day
Liver	Cholestatic hepatitis with constitutional symptoms	Prednisone, 20–40 mg/day Ursodiol, 15 mg/kg of body weight per day
Joints and muscles	Arthralgias	NSAID
	Granulomatous arthritis	Prednisone, 20–40 mg/day
	Myositis, myopathy	Prednisone, 20–40 mg/day
Hypercalciuria and hypercalcemia	Kidney stones, fatigue	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day

N Engl J Med 2007;357:2153-65.

Pulmonary sarcoidosis treatment algorithm.



Expert Rev Respir Med. 2020 Apr;14(4):391-403.

AMERICAN THORACIC SOCIETY DOCUMENTS

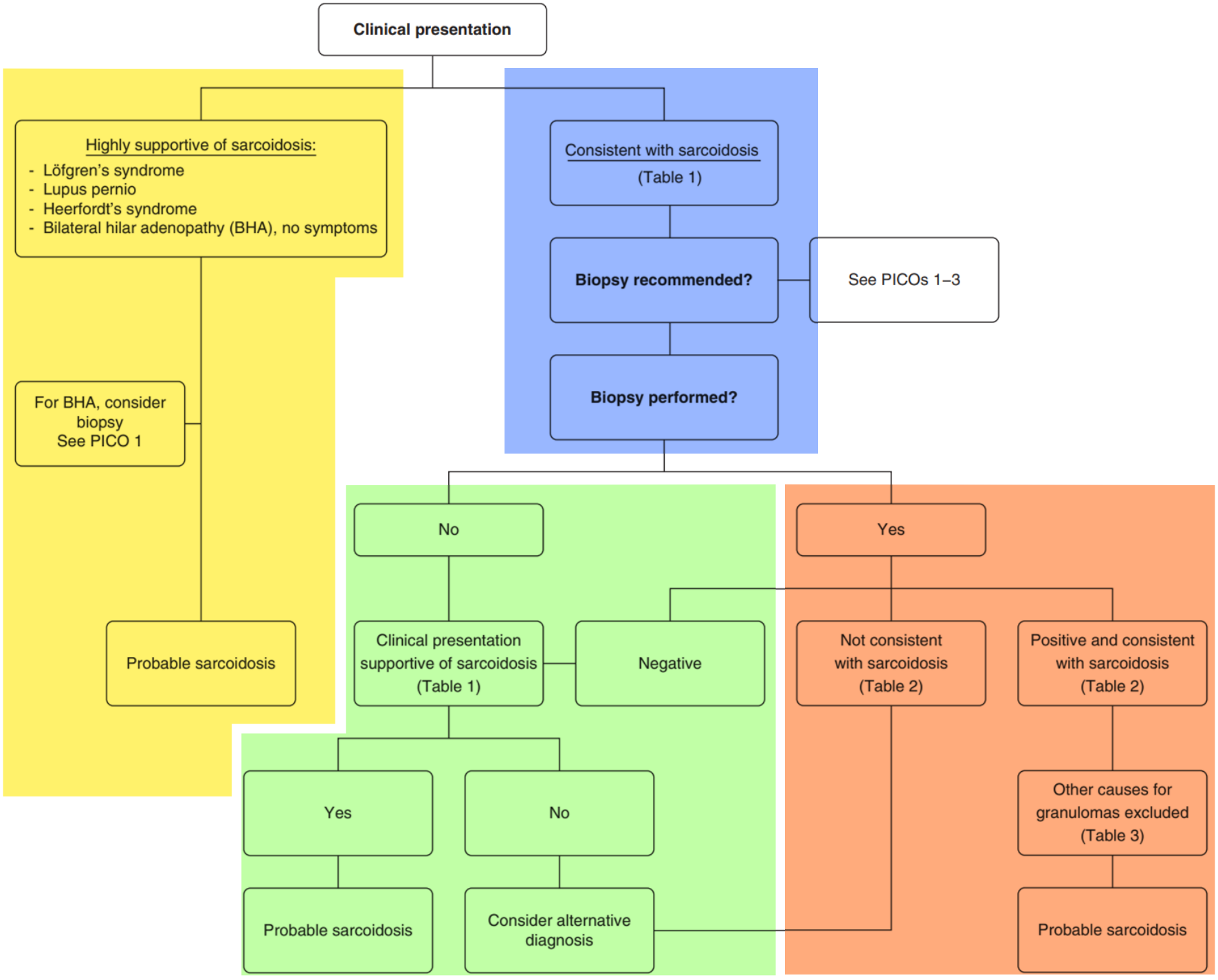
Diagnosis and Detection of Sarcoidosis

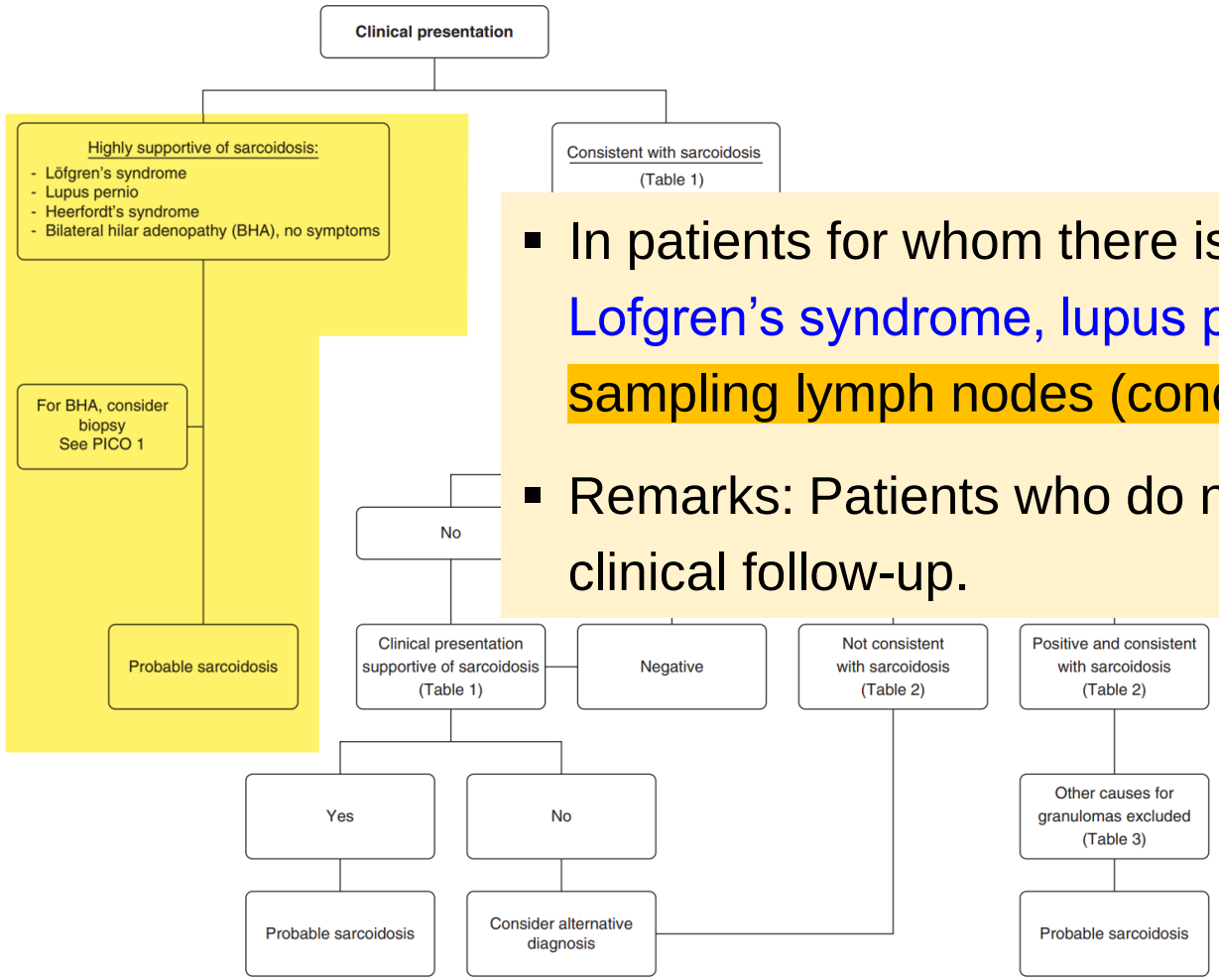
An Official American Thoracic Society Clinical Practice Guideline

Elliott D. Crouser*, Lisa A. Maier*, Kevin C. Wilson*, Catherine A. Bonham, Adam S. Morgenthau, Karen C. Patterson, Eric Abston, Richard C. Bernstein, Ron Blankstein, Edward S. Chen, Daniel A. Culver, Wonder Drake, Marjolein Drent, Alicia K. Gerke, Michael Ghobrial, Praveen Govender, Nabeel Hamzeh, W. Ennis James, Marc A. Judson, Liz Kellermeyer, Shandra Knight, Laura L. Koth, Venerino Poletti, Subha V. Raman, Melissa H. Tukey, Gloria E. Westney, and Robert P. Baughman; on behalf of the American Thoracic Society Assembly on Clinical Problems

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY FEBRUARY 2020

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020


Clinical presentation
Highly supportive of sarcoidosis:
- Löfgren's syndrome
- Lupus pernio
- Heerfordt's syndrome
- Bilateral hilar adenopathy (BHA), no symptoms
For BHA, consider biopsy
See PICO 1
Probable sarcoidosis
Consistent with sarcoidosis
(Table 1)
Biopsy recommended?
See PICOs 1–3
Biopsy performed?
No
Clinical presentation supportive of sarcoidosis
(Table 1)
Negative
Yes
No
Probable sarcoidosis
Consider alternative diagnosis
Yes
Not consistent with sarcoidosis
(Table 2)
Positive and consistent with sarcoidosis
(Table 2)
Other causes for granulomas excluded
(Table 3)
Probable sarcoidosis

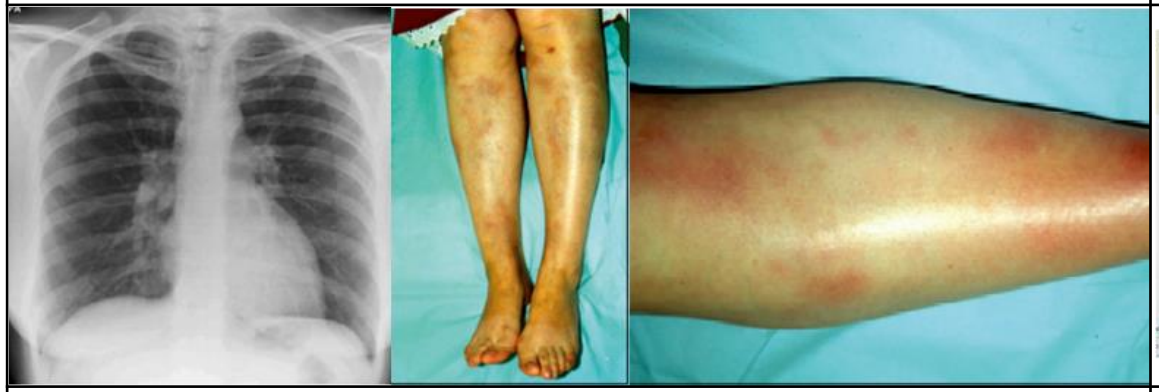
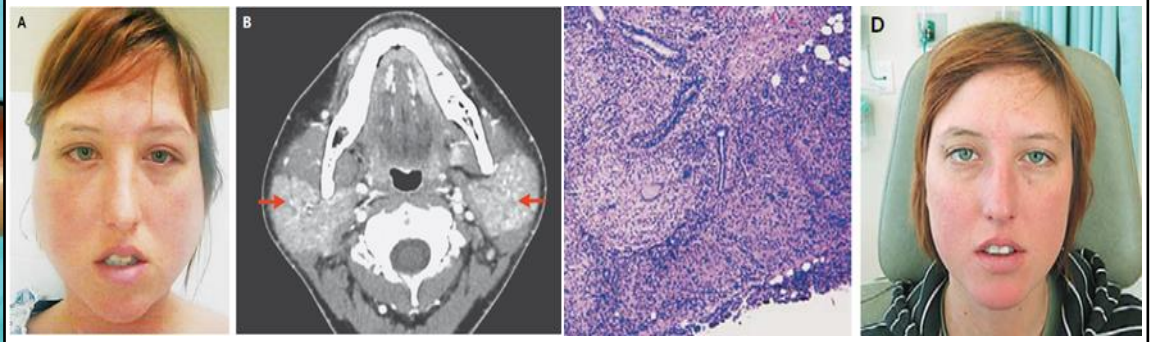


Highly supportive of sarcoidosis:
- Löfgren's syndrome
- Lupus pernio
- Heerfordt's syndrome
- Bilateral hilar adenopathy (BHA), no symptoms

- In patients for whom there is a high clinical suspicion for sarcoidosis (e.g., Lofgren's syndrome, lupus pernio, or Heerfordt's syndrome), we suggest NOT sampling lymph nodes (conditional recommendation, very low-quality evidence).
- Remarks: Patients who do not undergo lymph node sampling require close clinical follow-up.

Probable sarcoidosis

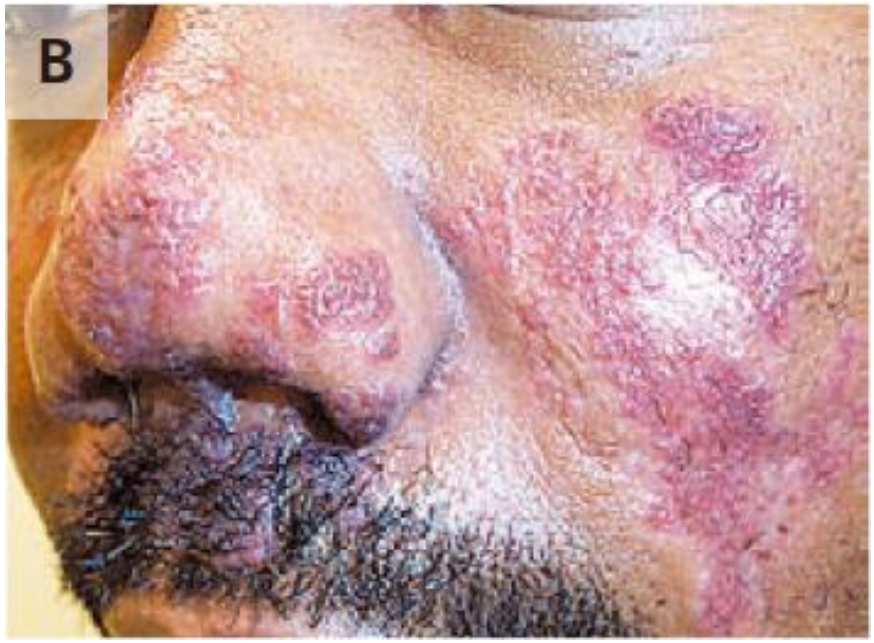
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Löfgren's syndrome White > Black, Asian	**Heerfordt's syndrome** 0.3 % of all cases of sarcoidosis
Bilateral hilar lymphadenopathy Erythema nodosum Arthritis	Parotitis Facial palsy Anterior uveitis Fever
	
Not usually require treatment EM: analgesics (paracetamol) Arthritis: NSAIDs, short course of oral steroid (PRD 15-40mg/day) Resolve spontaneously: 85% within 2years HLADRB1*0. (HLA-DR3) allele (good prognosis, 70-80%)	Treatment based on that for neurosarcoidosis Corticosteroids (1st choice)

Br J Hosp Med (Lond). 2015 Mar;76(3):154-8

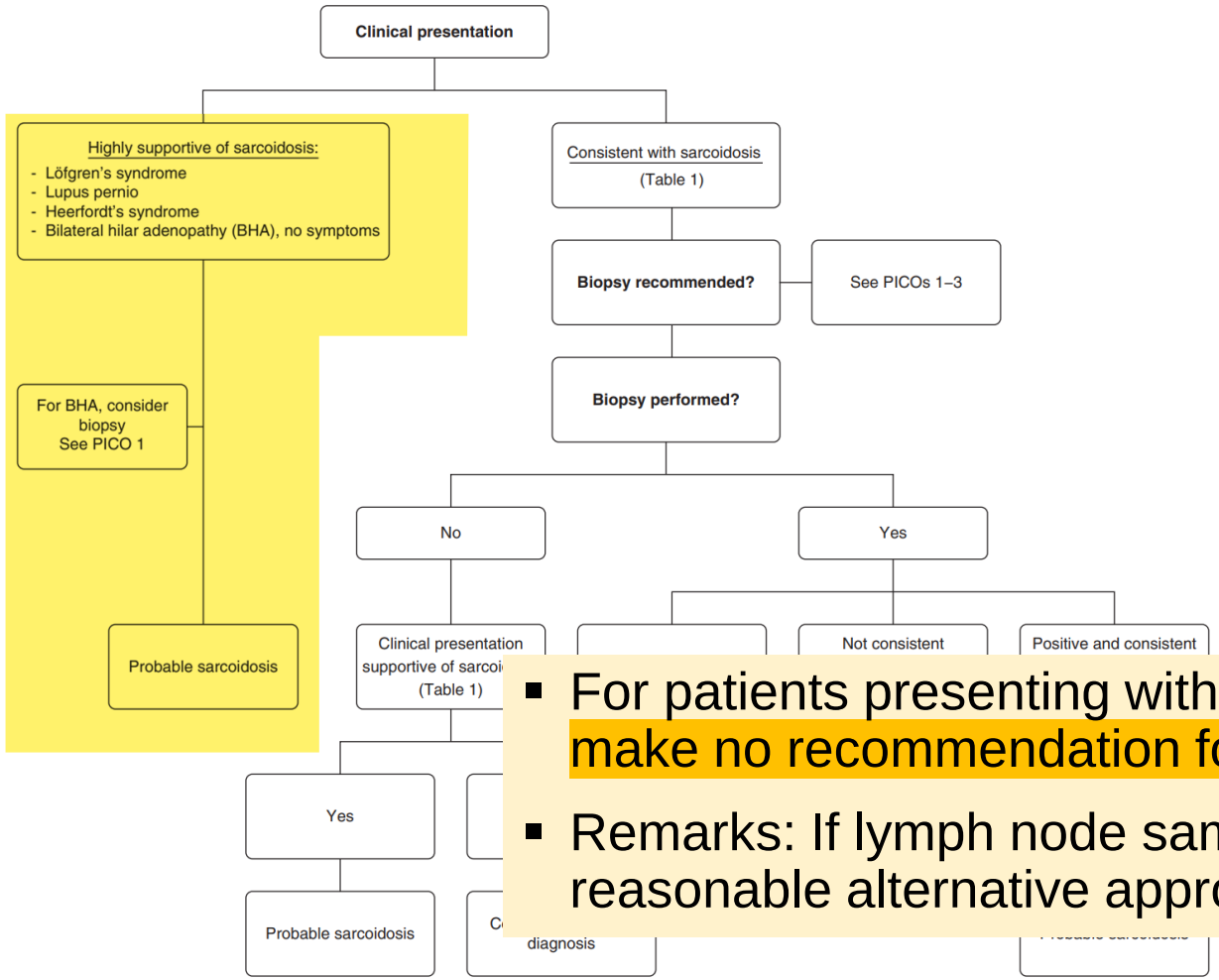
Case Rep Otolaryngol. 2016;2016:3642735
N Engl J Med. 2013 Aug 1;369(5):458

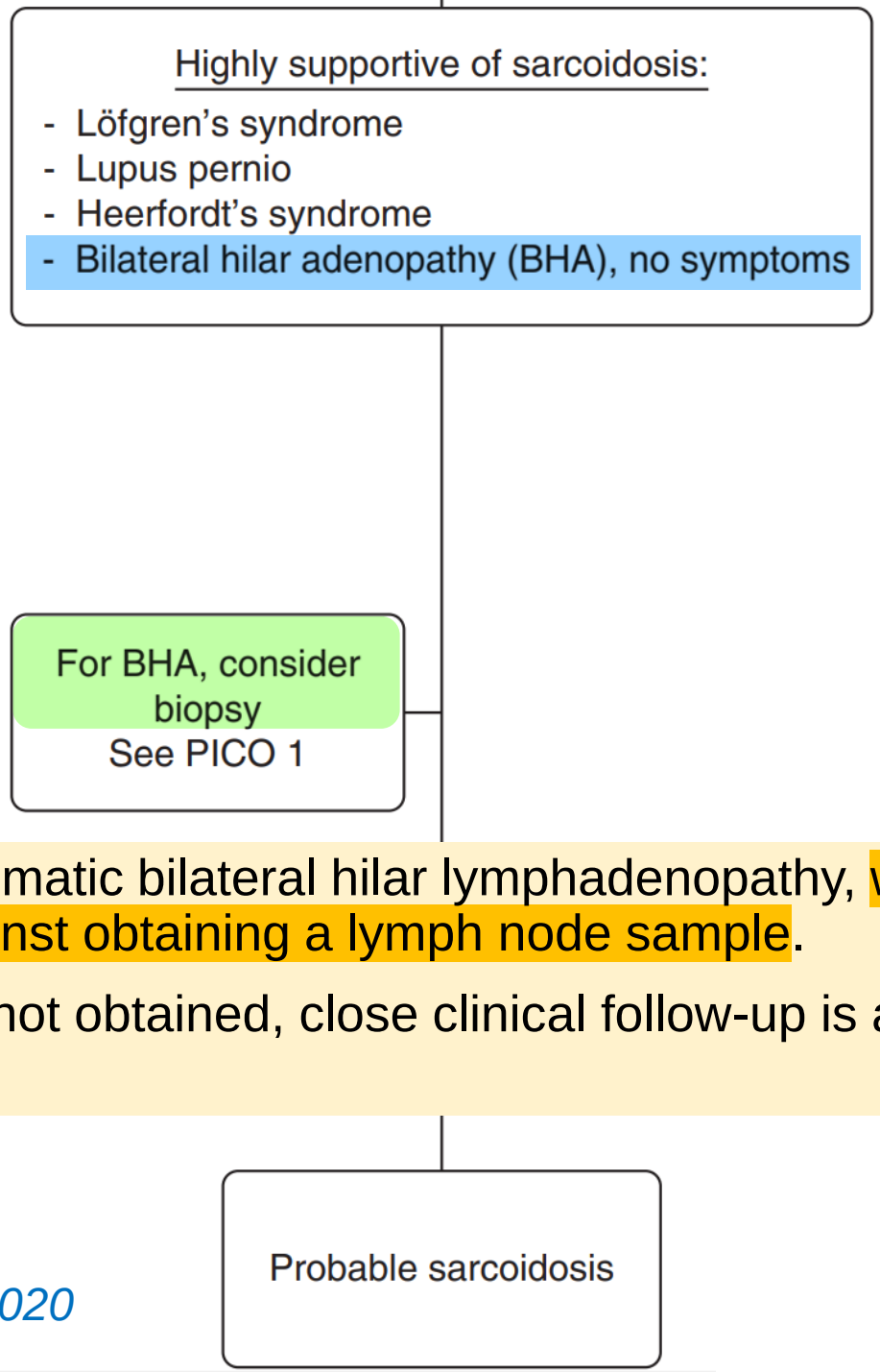
Lupus pernio



- Tend to affect African Americans and women disproportionately; associated with a chronic and refractory course, often requiring aggressive systemic treatment
- Smooth shiny plaques, which may become scaly
- Brown to violaceous or erythematous
- Centrofacial, especially on the nose, cheeks, lips, forehead, ears.
- Sarcoidosic involvement of the upper respiratory tract, bones (most commonly fingers and toes) and severe arthropathy are common.

Cells. 2021 Mar 31;10(4):766.

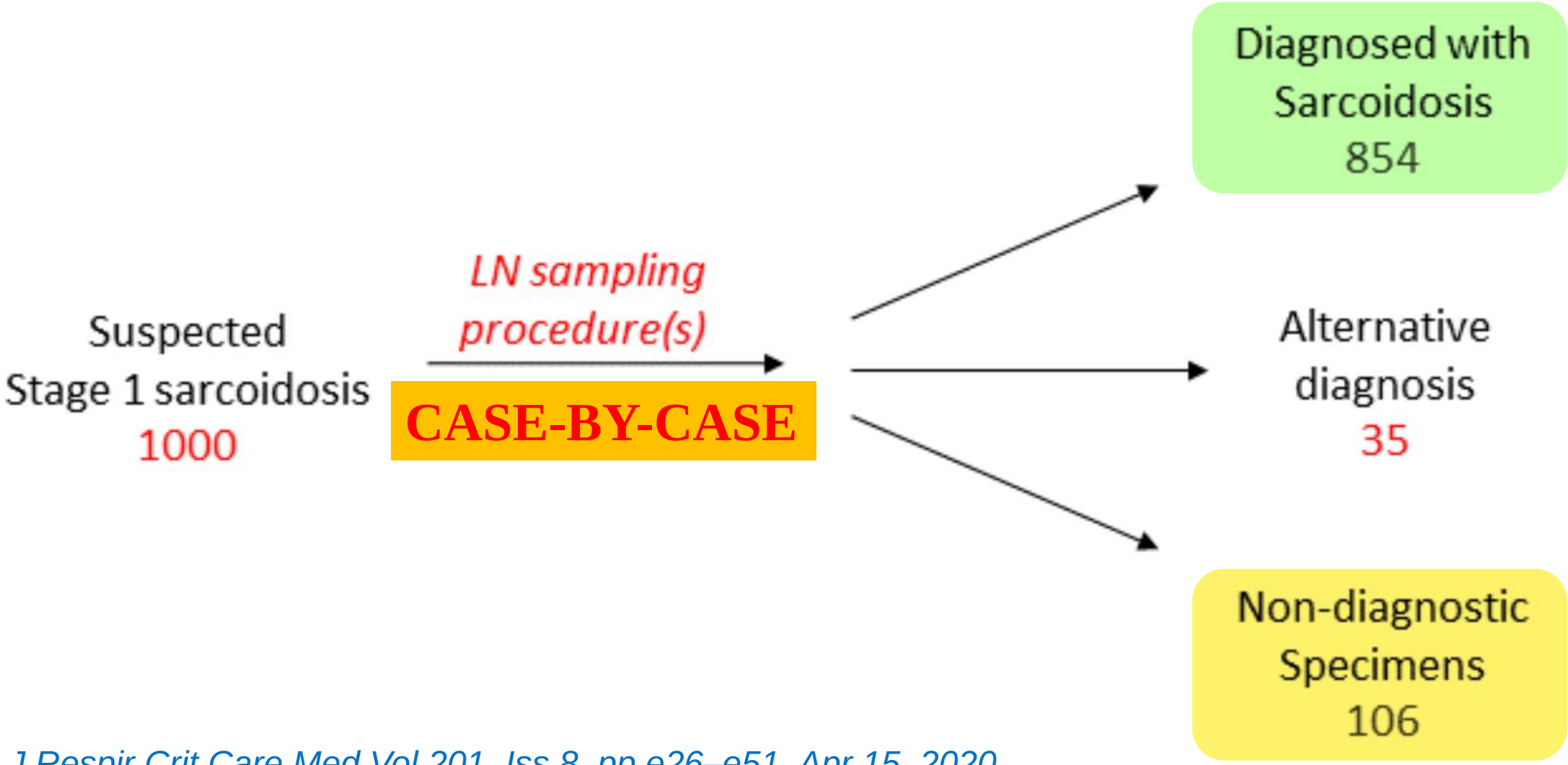




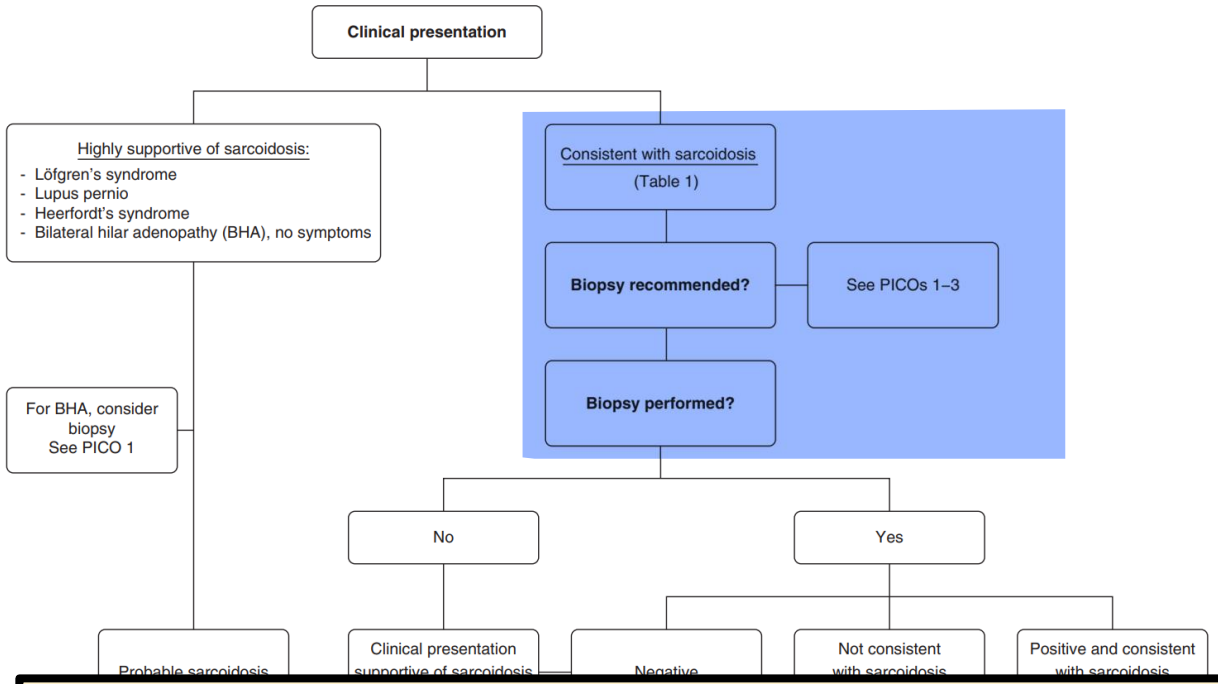
- For patients presenting with asymptomatic bilateral hilar lymphadenopathy, we make no recommendation for or against obtaining a lymph node sample.
- Remarks: If lymph node sampling is not obtained, close clinical follow-up is a reasonable alternative approach.

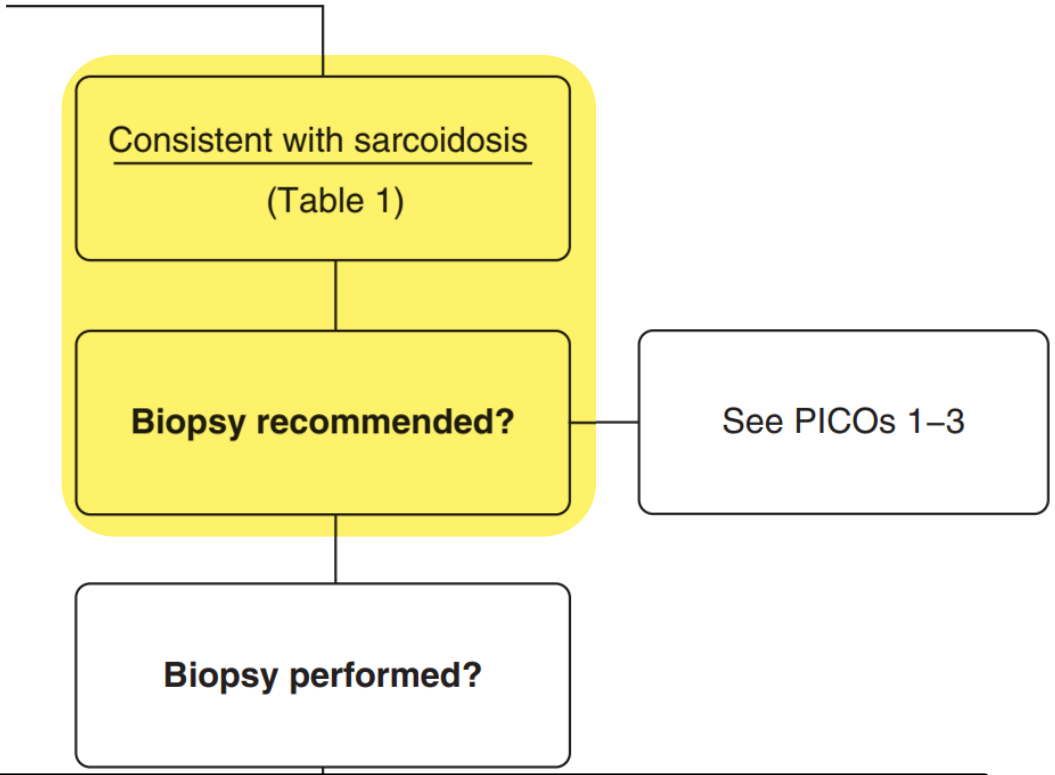
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Asymptomatic bilateral adenopathy



Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

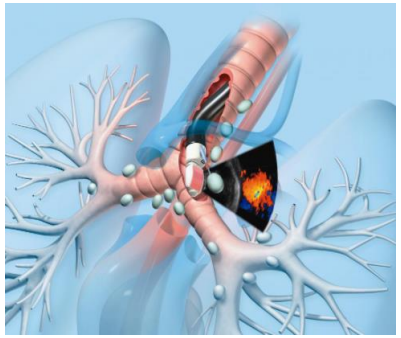




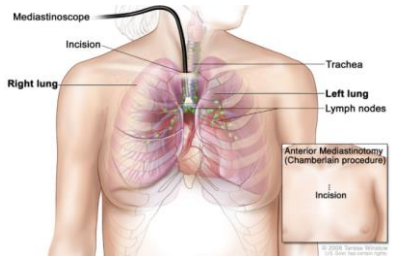
- For patients with suspected sarcoidosis and mediastinal and/or hilar lymphadenopathy for whom it has been determined that tissue sampling is necessary, we suggest endobronchial ultrasound (EBUS)-guided lymph node sampling, rather than mediastinoscopy, as the initial mediastinal and/or hilar lymph node sampling procedure (conditional recommendation, very low-quality evidence).

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Less complication
Less cost
More tolerable



EBUS-TBNA



Mediastinoscopy

Suspected Sarcoidosis 1000

EBUS guided lymph node sampling

Adequate Specimens 961

Diagnostic Specimens 826

Diagnosed with Sarcoidosis 801

Alternative Diagnosis 25

Inadequate Specimens 135

Inadequate Specimens 39

Mediastinoscopy

Adequate Specimens 1000

Diagnostic Specimens ?

Diagnosed with Sarcoidosis 958

Alternative diagnosis ?

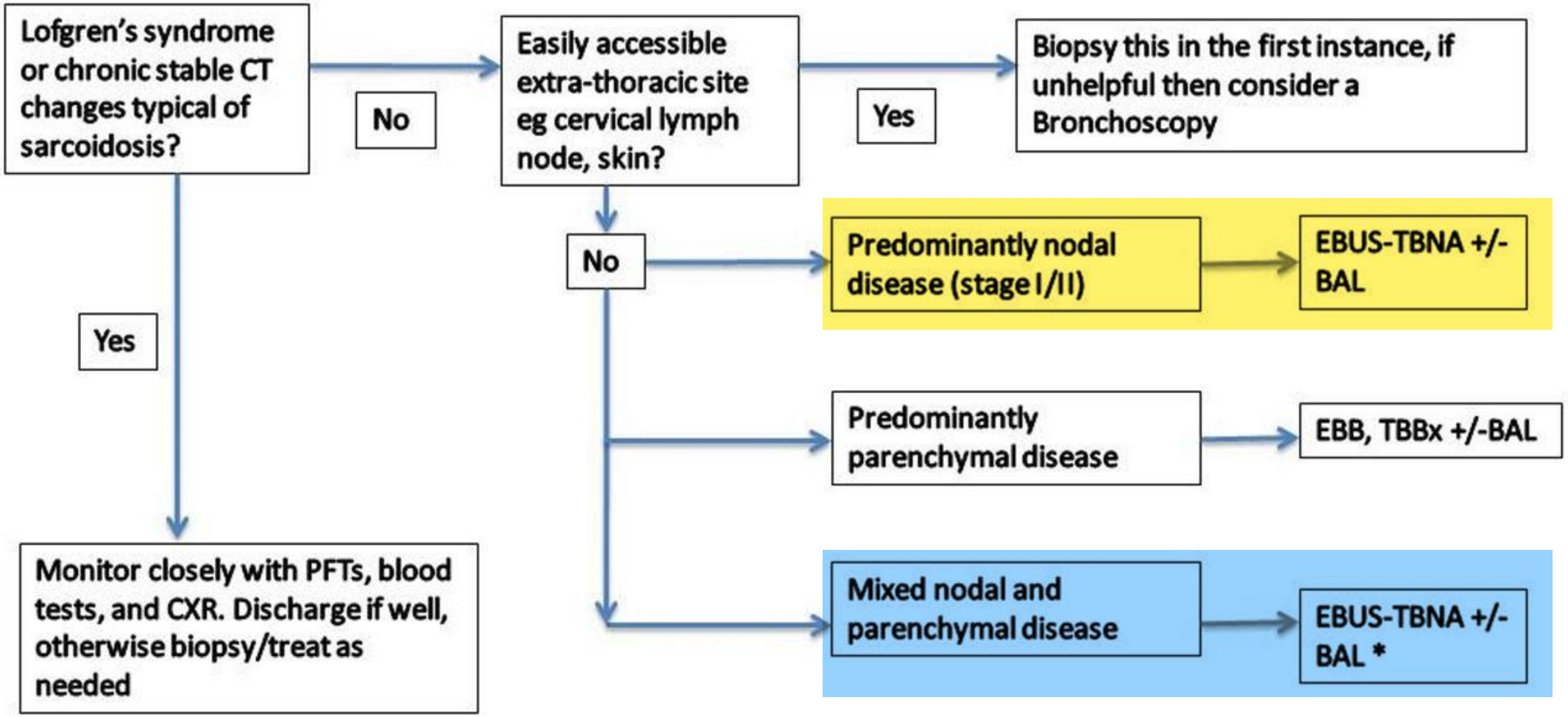
Non-diagnostic Specimens ?

Inadequate specimens 0

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Suggested algorithm for bronchoscopy in sarcoidosis

A combined EBUS-TBNA/TBBx may be indicated but need to consider the procedure time for a combined procedure.



Thillai M, et al. Thorax 2020;0:1–17.

1996-2014, single center, Korea

2007-2016, HIRA data, Korea

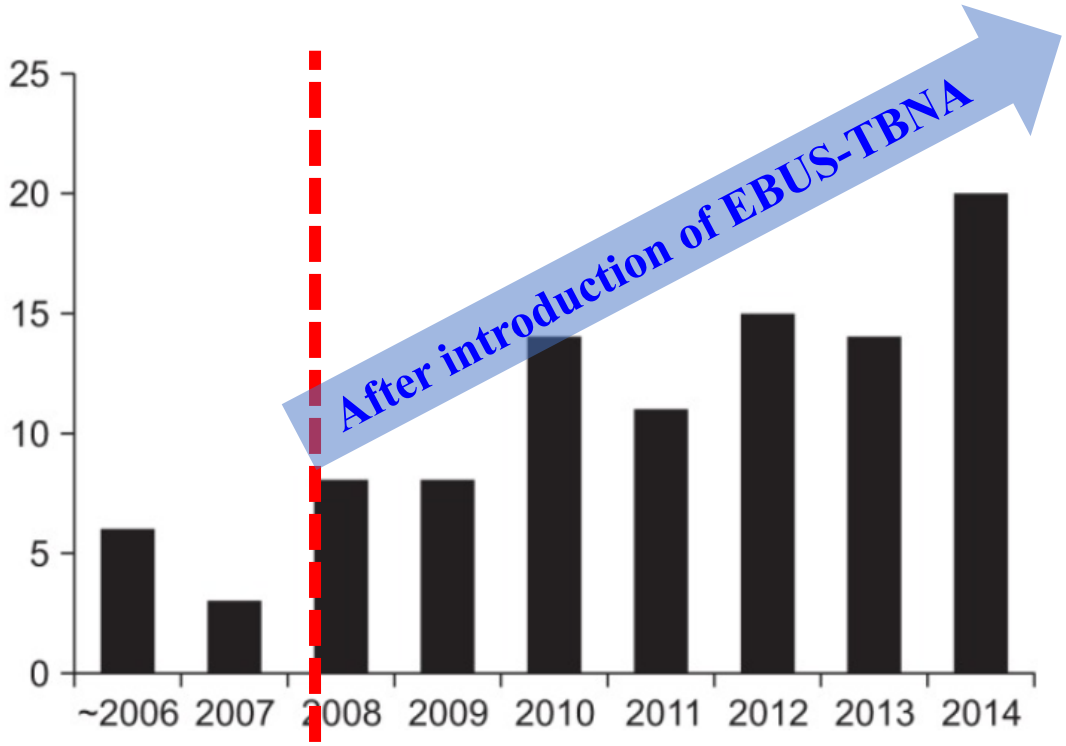


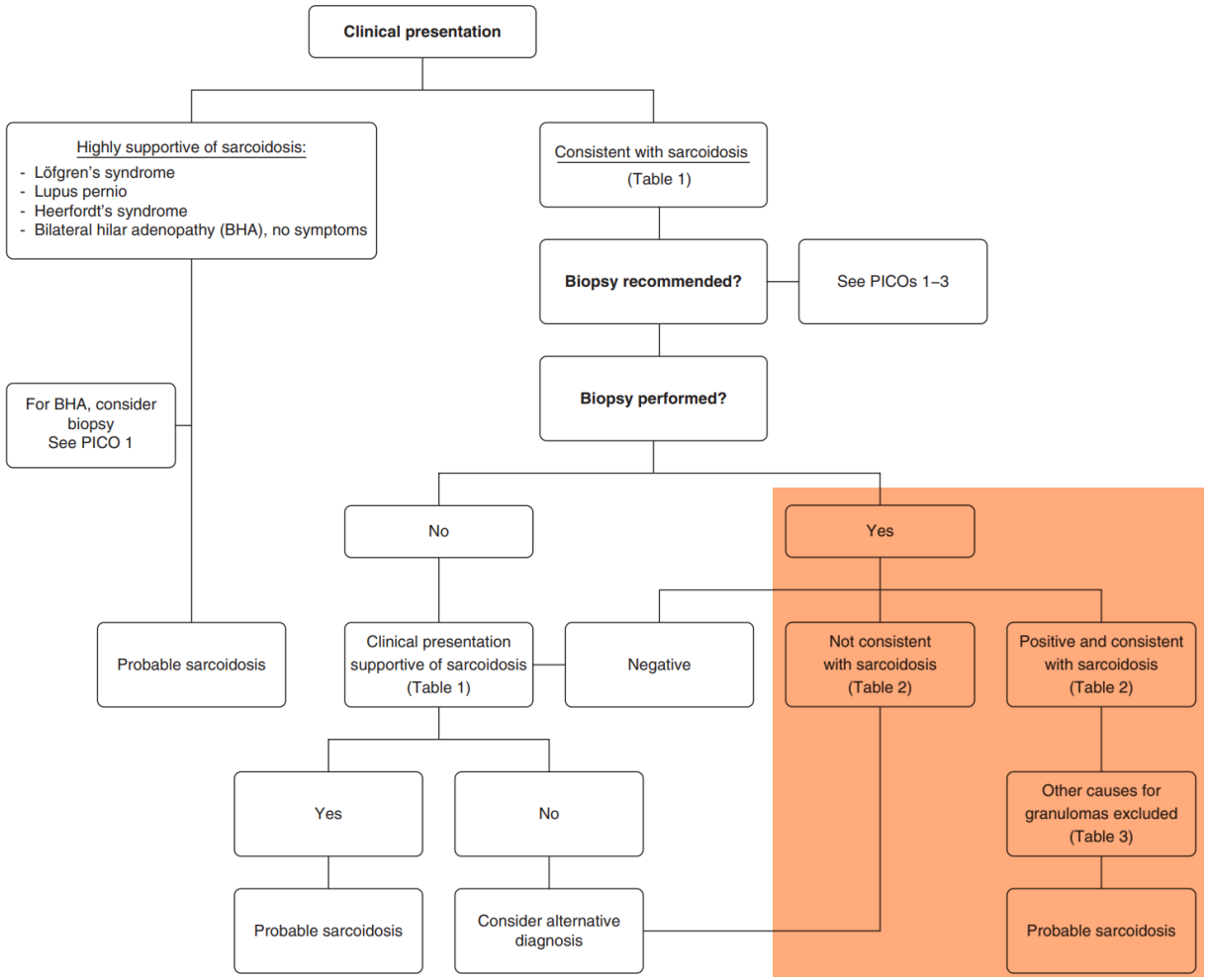
Table 1 Diagnostic methods of sarcoidosis

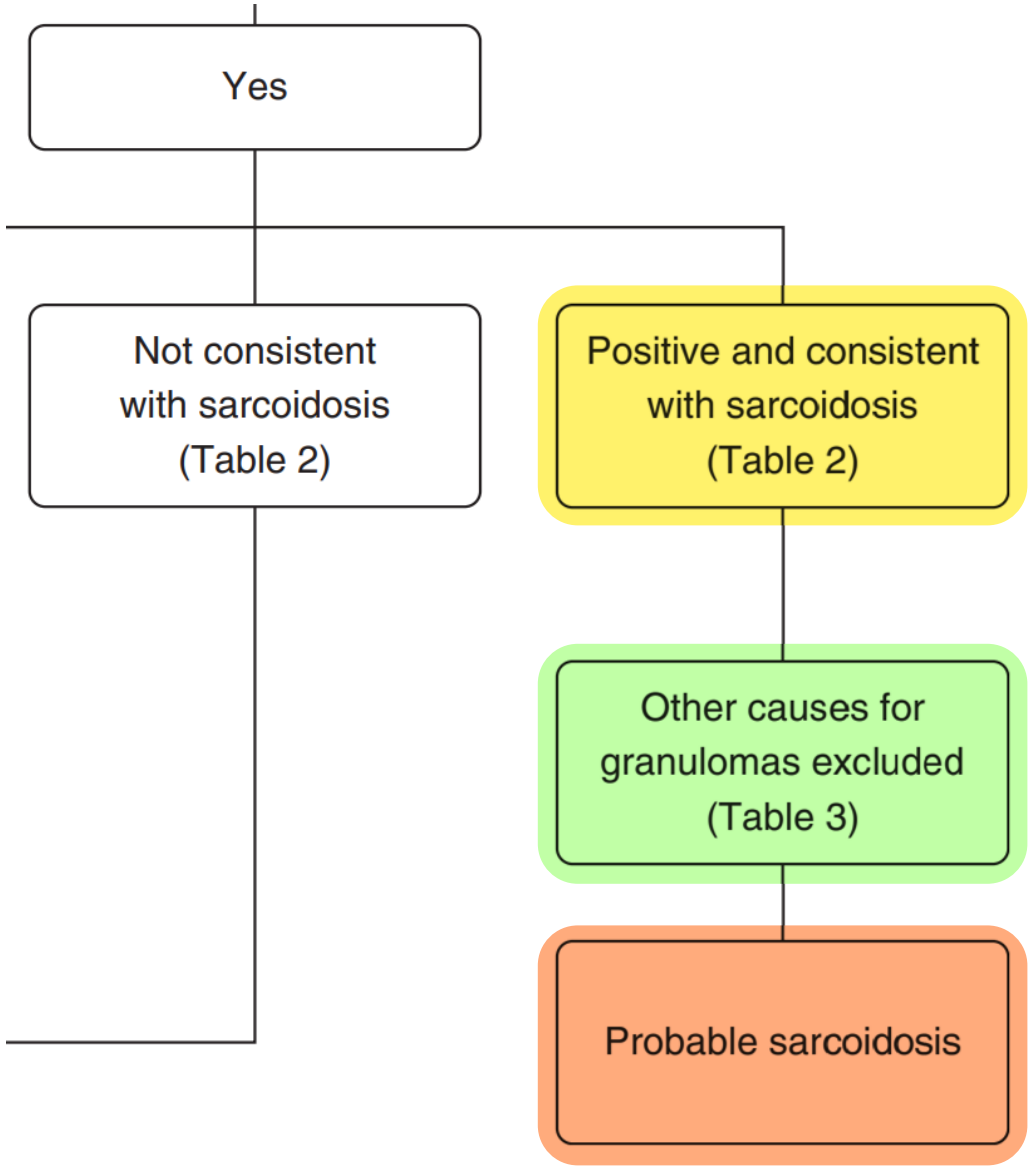
Diagnostic methods	N (%)
Bronchoscopy	1518 (50.6)
BAL	892 (29.7)
TBLB	504 (16.8)
Surgical lung biopsy	573 (19.1)
Skin biopsy	392 (13.1)
Musculoskeletal biopsy	45 (1.5)
Others[a]	293 (9.8)
All subjects undergoing biopsy	935 (51.3)
Unknown	796 (26.5)

BAL bronchoalveolar lavage, *TBLB* transbronchial lung biopsy
[a]Others included needle, incisional, and surgical biopsy of the liver, the heart, and organs other than the lung, skin, muscle, bone, and joints

Tuberc Respir Dis (Seoul). 2017 Jul; 80(3): 291–295.

Yoon et al. Respiratory Research (2018) 19:158





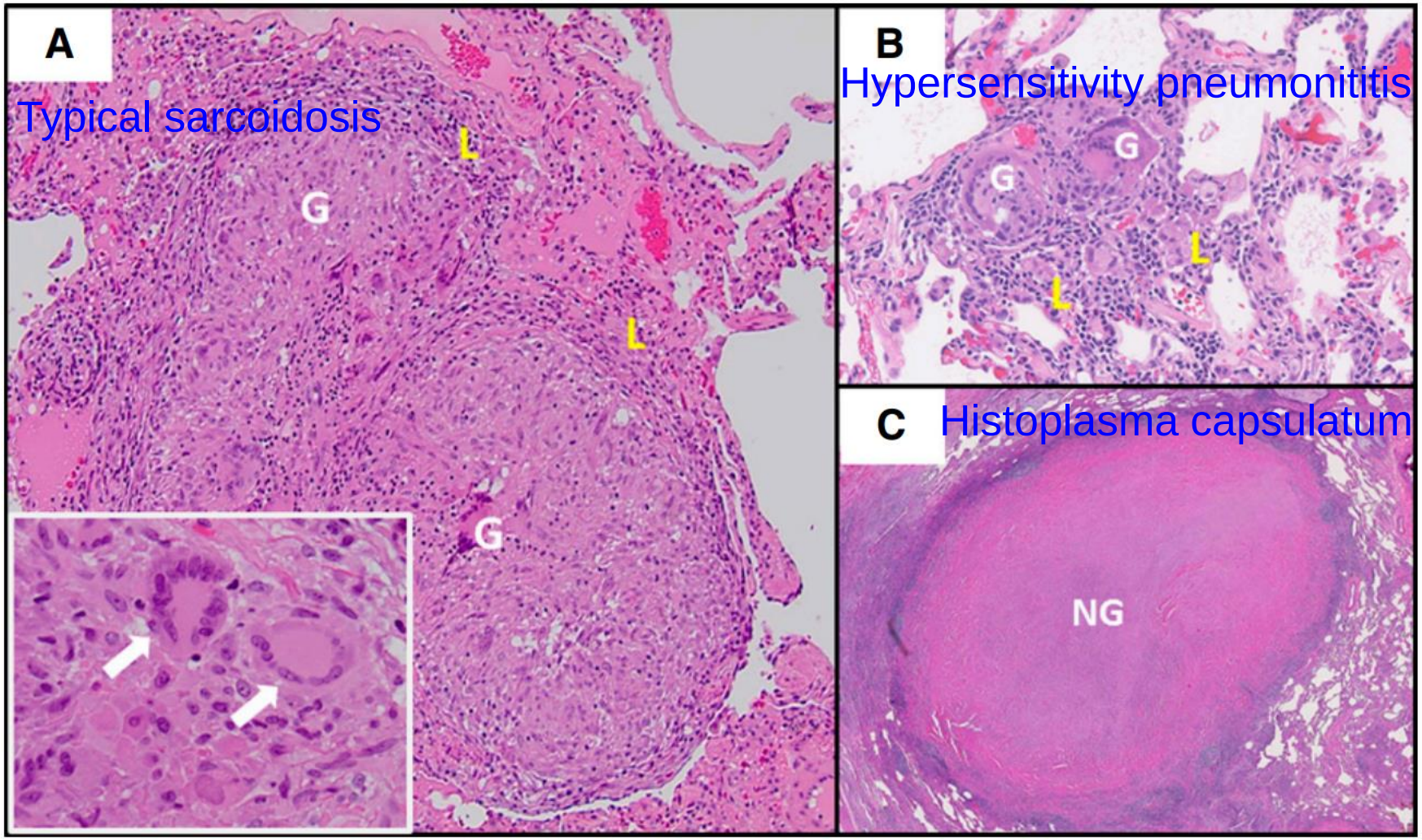
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Table 2. Key Pathological Features of Sarcoidosis

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Favors Sarcoidosis	Against Sarcoidosis
Granuloma presence	
Numerous	Few
Absent but with nodular hyalinized fibrosis representing healed granulomas (scattered multinucleated giant cells may be detectable)	Absent
Granuloma morphology	
Compact, tightly formed collections of large "epithelioid" histiocytes and multinucleated giant cells. Granulomas tend to stay discrete	Loosely organized collections of mononuclear phagocytes/ multinucleated giant cells
Nonnecrotic or focal and usually minimal ischemic necrosis	• Extensive necrosis • Dirty necrosis (containing nuclear debris) • Palisading granulomas
Fibrosis beginning at the granuloma periphery with extension centrally into the granuloma, with or without calcification	
Lesion location	
Perilymphatic; around bronchovascular bundles and fibrous septa containing pulmonary veins, and near visceral pleura	• Lack of lymphangitic distribution • Intraalveolar granulomas
In necrotizing sarcoid angiitis and granulomatosis: granulomatous angiitis with invasion of vascular walls	
Accompanying histology	
Sparse surrounding lymphocytic infiltrate	• Robust surrounding inflammatory infiltrate (including lymphocytes, neutrophils, eosinophils, and plasma cells) • Secondary lymphoid follicles
Microorganism stains and cultures	
Negative	Positive
Multidisciplinary clinical features	
Intra- and extrathoracic involvement	Extrathoracic involvement only

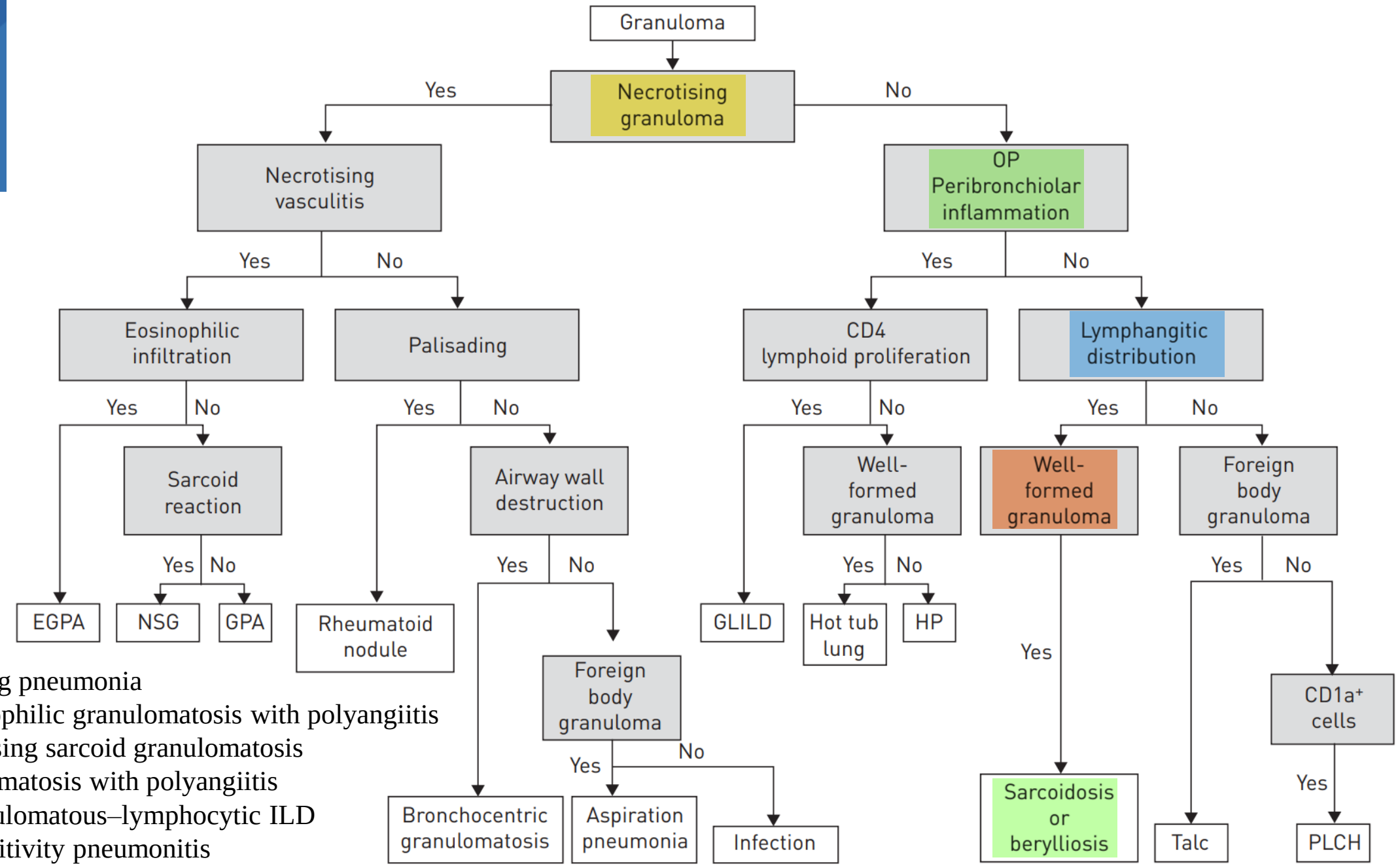
Comparison of pulmonary sarcoidosis granuloma histology to other granulomatous lung diseases.



Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

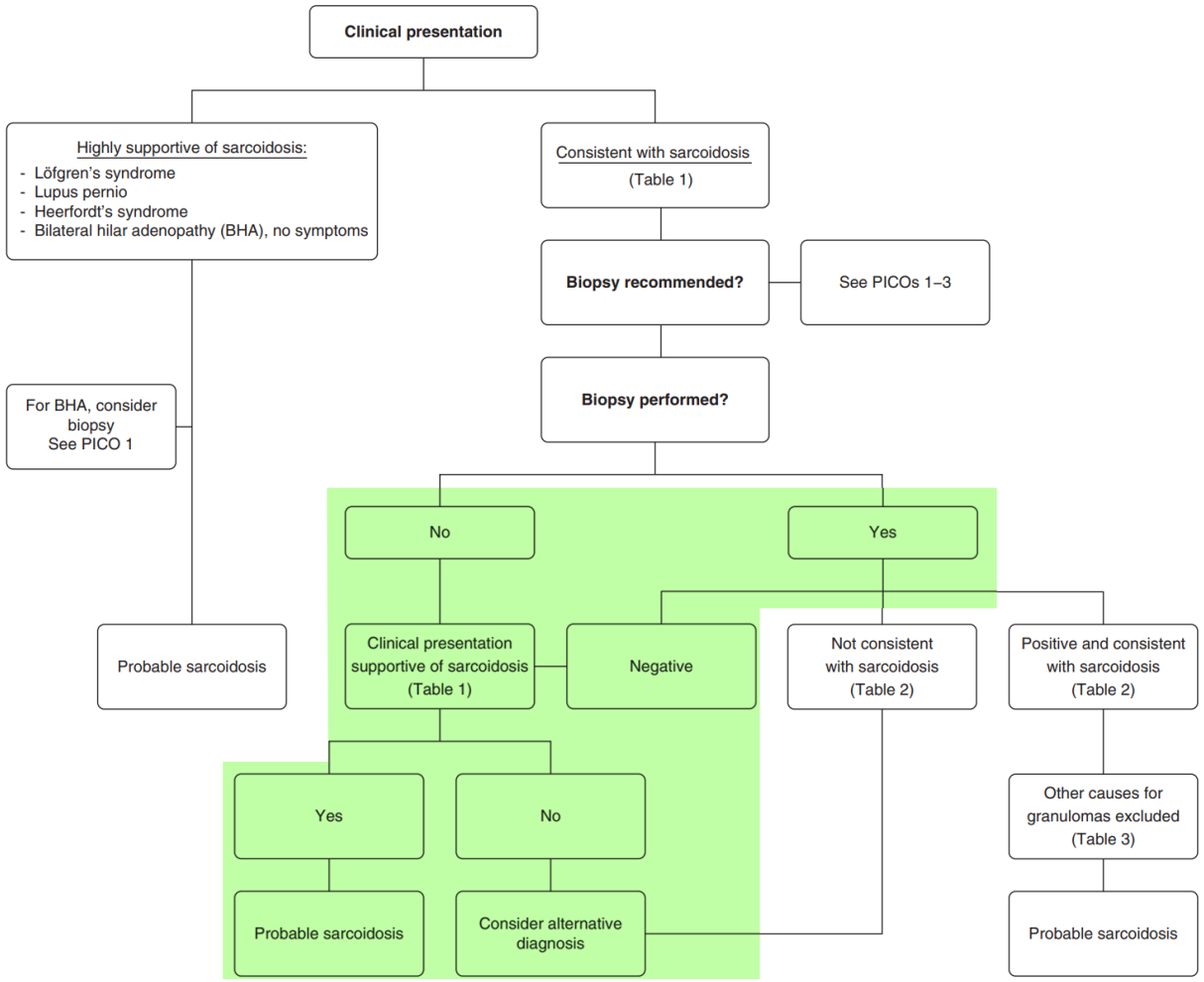
	Granulomatous Lesion within These Sites:					
	Lung	Lymph Node	Skin	Liver	Bone Marrow	Testing and Clinical Pearls
Infectious etiologies						
Bacteria						
Tuberculosis*	X	X	X	X	X	Culture is diagnostic gold standard; IFN-γ release assay used for screening, and preferable to tuberculin skin testing due to anergy
Nontuberculous mycobacteria (MAC and *M. kansasii*)*	X	X	X	X	X	Culture is the gold standard
Aspiration pneumonia*	X					Culture
Brucella		X	X	X	X	Serum agglutination and ELISA; livestock exposure history
Tropheryma whippelii		X		X		Periodic acid–Schiff stain; immunohistochemistry testing; diarrhea, weight loss, and joint pains
Mycobacterium leprae			X			Culture is the gold standard, but can be difficult; histology; PCR
Francisella tularensis		X	X			Serologic assay, then repeat in 2 wk; rabbit exposure
Bartonella henselae		X	X			Titers >1:256; cat exposure
Coxiella burnetii				X	X	Serology; PCR; livestock exposure
Fungi						
*Aspergillus**	X		X		X	Culture; *Aspergillus* IgG; histology
*Histoplasma**	X	X	X		X	Culture; urine histoplasma antigen
*Blastomyces**	X		X			Culture; histology; blasto Ag is nonspecific
*Coccidioides**	X				X	Serologic tests using EIA for IgM and IgG; then confirmatory immunodiffusion
Cryptococcus	X		X	X	X	Cryptococcal serum antigen
Pneumocystis	X					Histology; screen with β-D-glucan assay
Viruses						
Herpes zoster	X		X			Granulomas may occasionally be found
Parasitic						
Toxoplasma gondii		X	X	X		Toxoplasma serologic assay IgM and IgG
Schistosomiasis	X		X	X		Serology and microscopic visualization of eggs in stool or urine
Leishmaniasis			X	X		Histology and PCR for *Leishmania*
Echinococcosis			X	X		EIA; ultrasound imaging
Enterobius			X	X		Pinworm paddle test, then microscopy
Dirofilaria	X					Histology; eosinophilia
Noninfectious etiologies						
Malignancy						
Lymphoma*	X	X	X	X	X	Clonal cell population; rarely can have elevated serum ACE
Sarcoid-like reaction to tumor*	X	X	X	X	X	PET useful for selecting biopsy site but not diagnostic; biopsy must be performed to diagnose
Lymphomatoid granulomatosis			X			Atypical clonal EBV-positive B cells; multiple pulmonary nodules with lymphocytic transmural angiitis and granulomas noted sometimes in skin
Germ cell tumor		X				Serum α fetoprotein, human chorionic gonadotropin, lactate dehydrogenase
Autoimmune or immune dysfunction						
ANCA-associated vasculitides (GPA, MPA, and EGPA)	X		X			MPO or PR3 ANCA+, renal disease, necrotizing vasculitis; eosinophilic infiltration if EGPA
GLILD associated with CVID	X	X				Nonnecrotizing granulomas, LIP, and follicular bronchiolitis on lung biopsy; hypogammaglobulinemia and recurrent infections
Rheumatoid nodules			X			Multiple subpleural nodules in patient with anti-CCP antibodies, arthralgias; necrotizing granulomas
Langerhans cell histiocytosis	X	X	X	X	X	Young smoker; multiple bizarre-shaped upper lung zone cysts and/or nodules; Langerhans cell stain CD1a and S100 positive; eosinophilic granulomas most common
IgG4-related disease	X	X	X	X	X	Elevated serum IgG4; elevated tissue IgG4+ plasma cell count and IgG4:IgG ratio; granulomas rare; differential diagnosis with multicentric Castleman disease
Inflammatory bowel disease	X		X	X		GI symptoms; granulomatous bronchiolitis
Primary biliary cholangitis				X		Cholestasis; antimitochondrial antibodies; portal based, poorly formed granulomas with bile duct destruction
Primary sclerosing cholangitis				X		Cholestasis; P-ANCA+; ulcerative colitis associated; biliary strictures present, granulomas rare and not associated with bile duct destruction
Autoimmune hepatitis						Abnormal liver function tests and autoantibodies (e.g., anti–smooth muscle); syncytial multinucleated giant cells are rare in adults but may be observed in children or adolescents
Exposures						
Hypersensitivity pneumonitis*	X	X				Organic exposure, small poorly formed interstitial granulomas in interstitium, prominent lymphocytic infiltrates, chronic inflammatory infiltrates accentuated around bronchioles
Hot tub lung syndrome (MAC exposure with hypersensitivity features)	X	X				Aerosolized water exposure, MAC cultured from sputum, lung or hot tub, large well-formed granulomas in bronchiole lumens
Pneumoconiosis (such as beryllium, titanium, aluminum, zirconium, cobalt, and others)	X	X	X			Inorganic exposure history
Drug-induced granulomatous disease (including but not limited to IFN, checkpoint inhibitor, anti-TNF, and/or biologic therapies)*	X	X	X	X	X	Usually nonnecrotizing granulomas. Drug exposure history essential. *See* www.pneumotox.com for full list
Foreign body granulomatosis (such as talc aspirated or injected, tattoo ink)*	X	X	X			Serum ACE elevated in many patients; particles found on biopsy; perivascular granulomas
Steatosis (lipogranulomas)				X		Central lipid vacuole; ingestion of mineral oil or hepatic steatosis
Idiopathic						
Sarcoidosis	X	X	X	X	X	Multisystemic; well formed, usually nonnecrotic granulomas
Necrotizing sarcoid granulomatosis	X	X				Granulomatous pneumonitis with necrosis and vasculitis; multiple necrotic lung nodules
Histiocytic necrotizing lymphadenitis (Kikuchi's disease)		X				Cervical lymphadenopathy and low-grade fever. Granulomas are not found, although necrotic areas with histiocytes are present
GLUS		X	X	X	X	Lacks progressive lung parenchymal disease, elevated serum calcium, 1,25-dihydroxyvitamin D, and ACE
Bronchocentric granulomatosis	X					Associated with asthma and *Aspergillus* infection in 50%. Necrotizing granulomas exclusively in bronchi and bronchioles

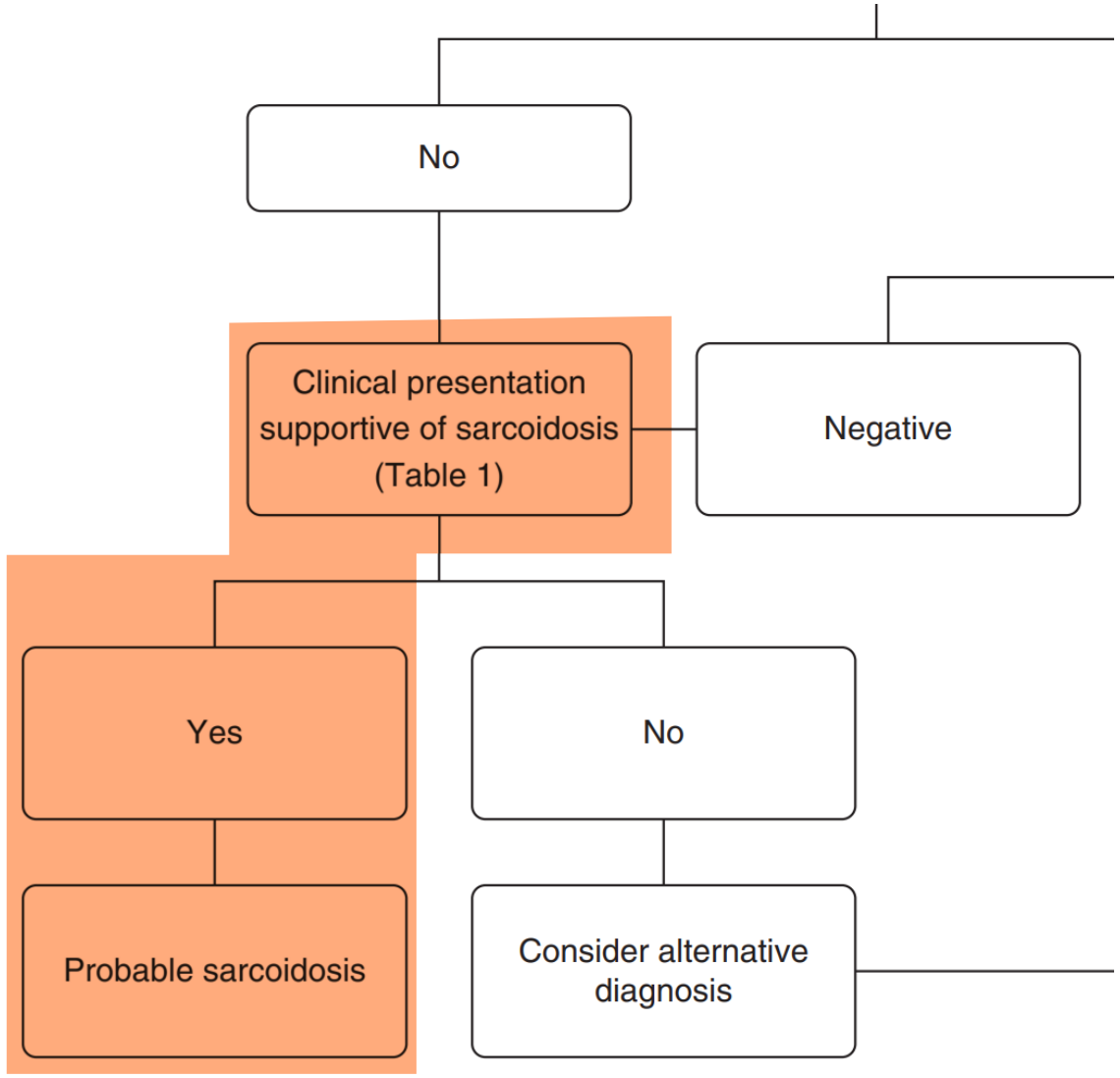
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020



OP: organising pneumonia
EGPA: eosinophilic granulomatosis with polyangiitis
NSG: necrotising sarcoid granulomatosis
GPA: granulomatosis with polyangiitis
GLILD: granulomatous–lymphocytic ILD
HP:hypersensitivity pneumonitis
PLCH: pulmonary Langerhans cell histiocytosis

Eur Respir Rev 2017; 26: 170012



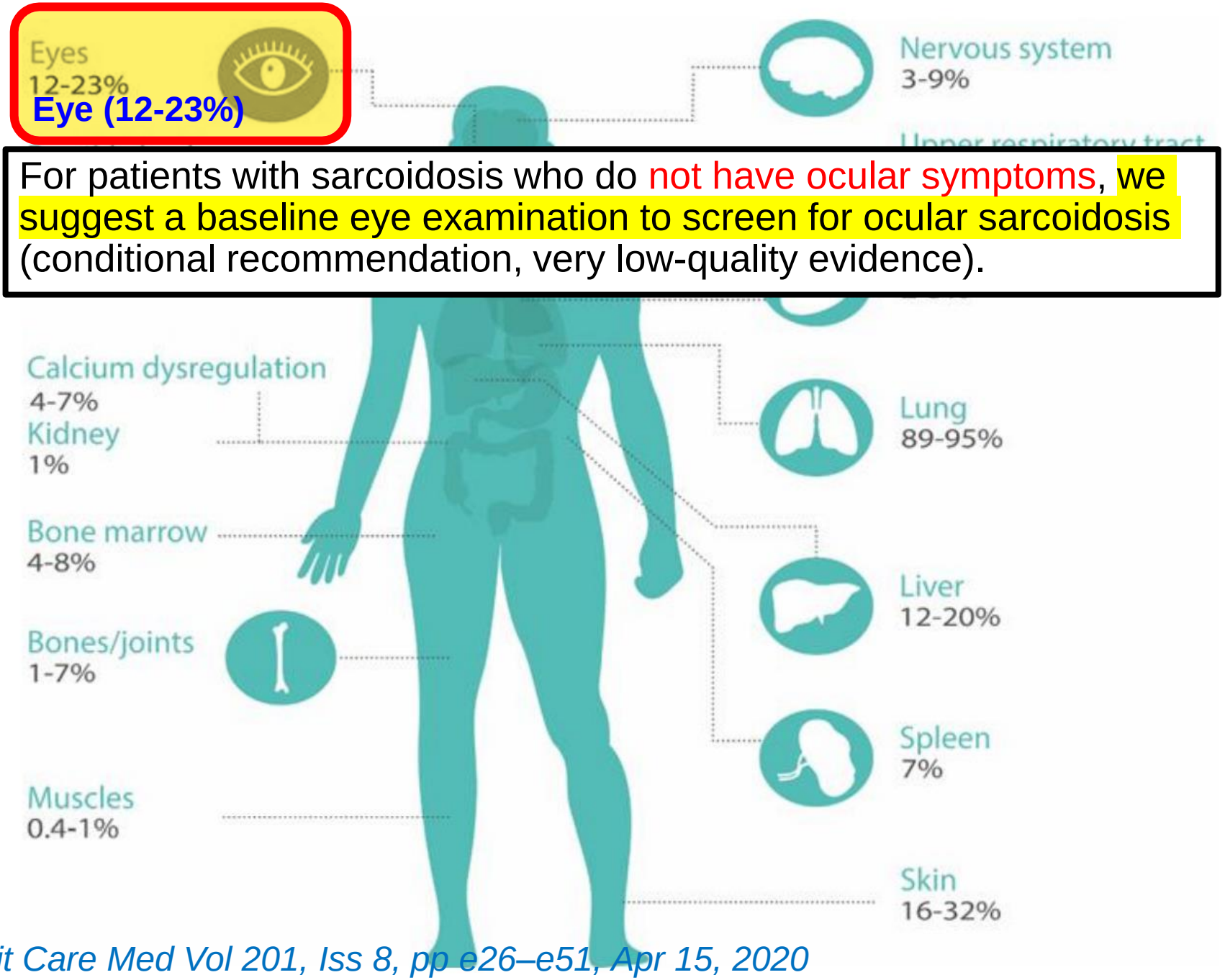


Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Table 1. Clinical Features Supportive of a Diagnosis of Sarcoidosis

	Highly Probable	Probable
History	Löfgren's syndrome*	Seventh cranial nerve paralysis Treatment-responsive renal failure Treatment-responsive CM or AVNB Spontaneous/inducible VT with no risk factors
Physical	Lupus pernio Uveitis Optic neuritis Erythema nodosum	Maculopapular, erythematous, or violaceous skin lesions Subcutaneous nodules Scleritis Retinitis Lacrimal gland swelling Granulomatous lesions on direct laryngoscopy Symmetrical parotid enlargement Hepato-/splenomegaly
Imaging	Bilateral hilar adenopathy (CXR, CT, and PET) Perilymphatic nodules (chest CT) Gadolinium enhancement on MRI (CNS) Osteolysis, cysts/punched-out lesion, trabecular pattern bone (X-ray, CT, and MRI) Parotid uptake (gallium and PET)	Upper lobe or diffuse infiltrates (CXR, CT, and PET) Peribronchial thickening (CT) Two or more enlarged extra thoracic nodes (CT, MRI, and PET) Increased inflammatory activity in heart (MRI, PET, and gallium) Imaging showing enlargement or nodules in liver or spleen (CT, PET, and MRI) Inflammatory lesions in bone (gallium, PET, and MRI)
Other testing	Hypercalcemia or hypercalciuria with abnormal vitamin D metabolism†	Reduced LVEF with no risk factors (echo and MRI) Elevated ACE level test‡ Nephrolithiasis with calcium stone, no vitamin D testing BAL lymphocytosis or elevated CD4:CD8 ratio Alkaline phosphatase greater than three times the upper limit of normal New-onset, third-degree AV block in young or middle-aged adults

In patients with sufficient tissue to rule out lymphoma and carcinoma….(BTS guideline)

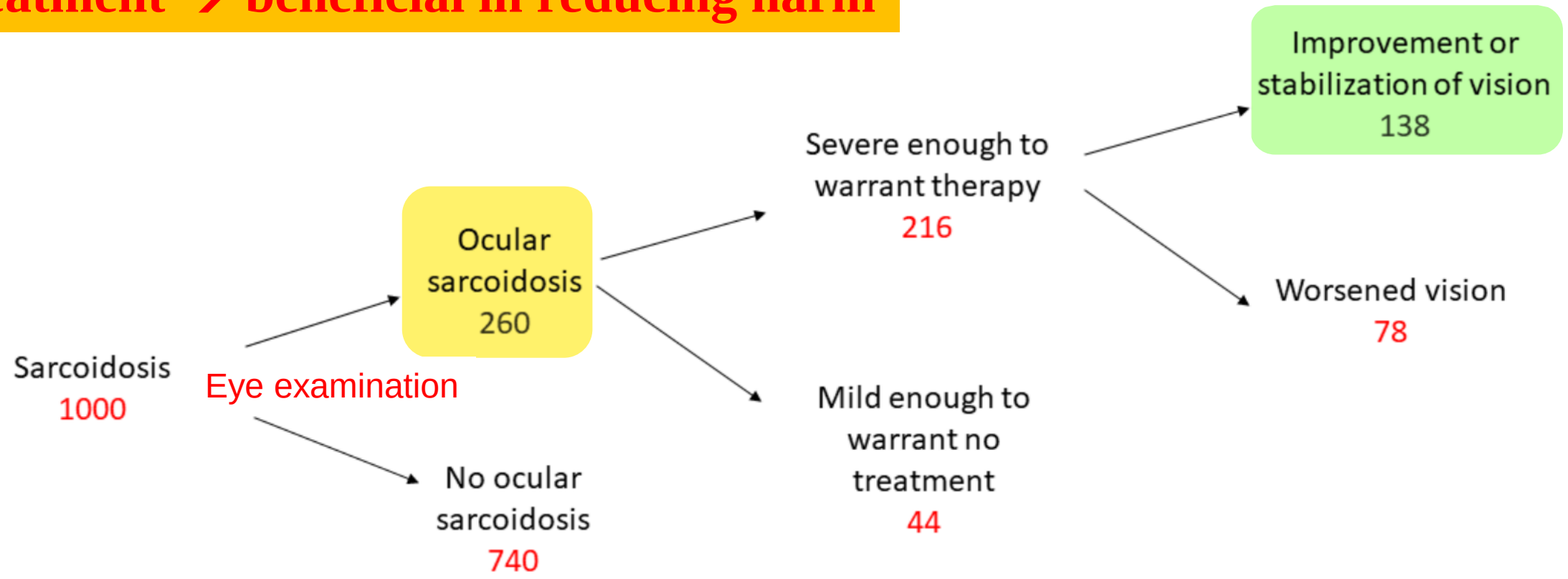


For patients with sarcoidosis who do not have ocular symptoms, we suggest a baseline eye examination to screen for ocular sarcoidosis (conditional recommendation, very low-quality evidence).

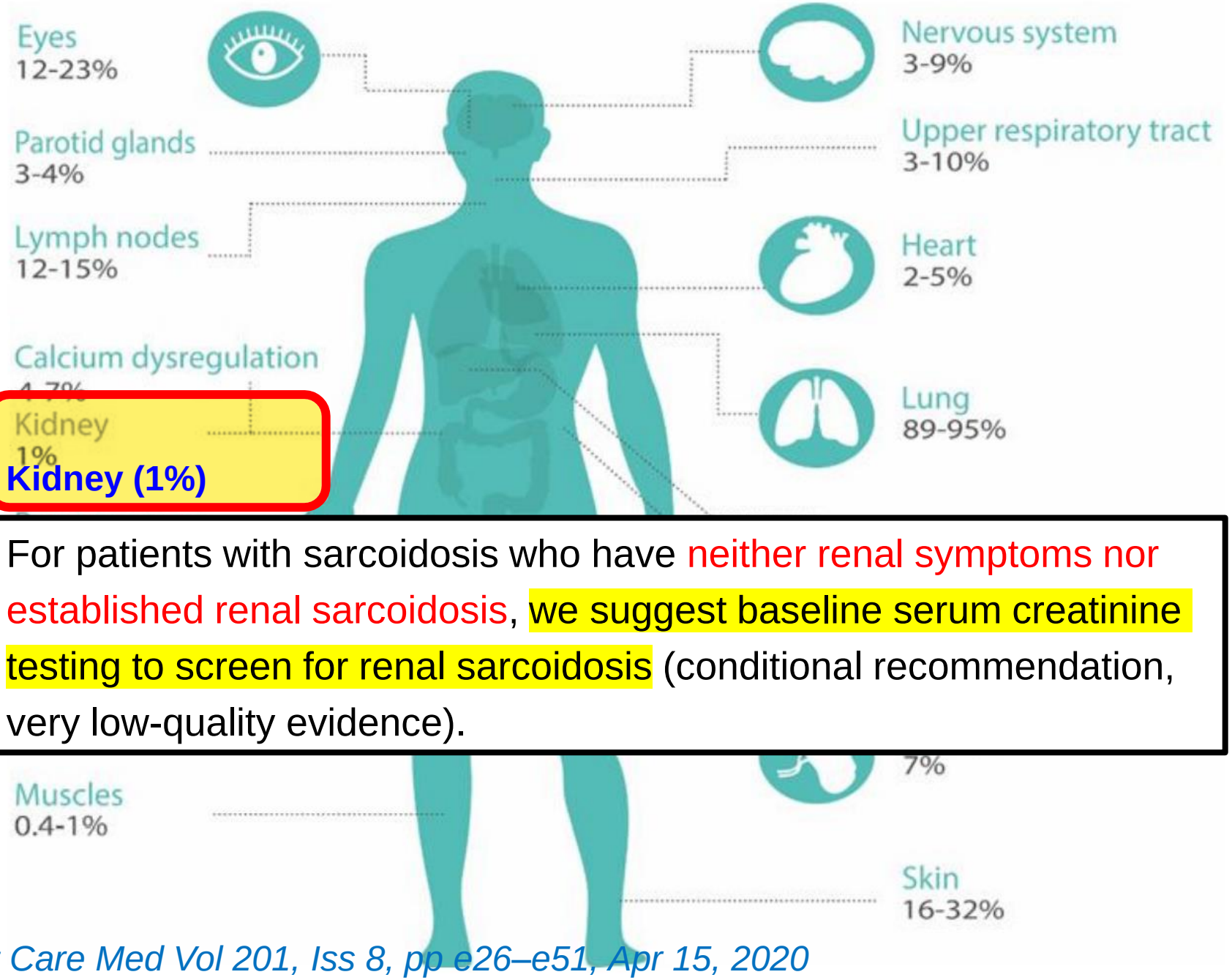
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Screening for Ocular Sarcoidosis by Routine Eye Examination

Treatment → beneficial in reducing harm



Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020



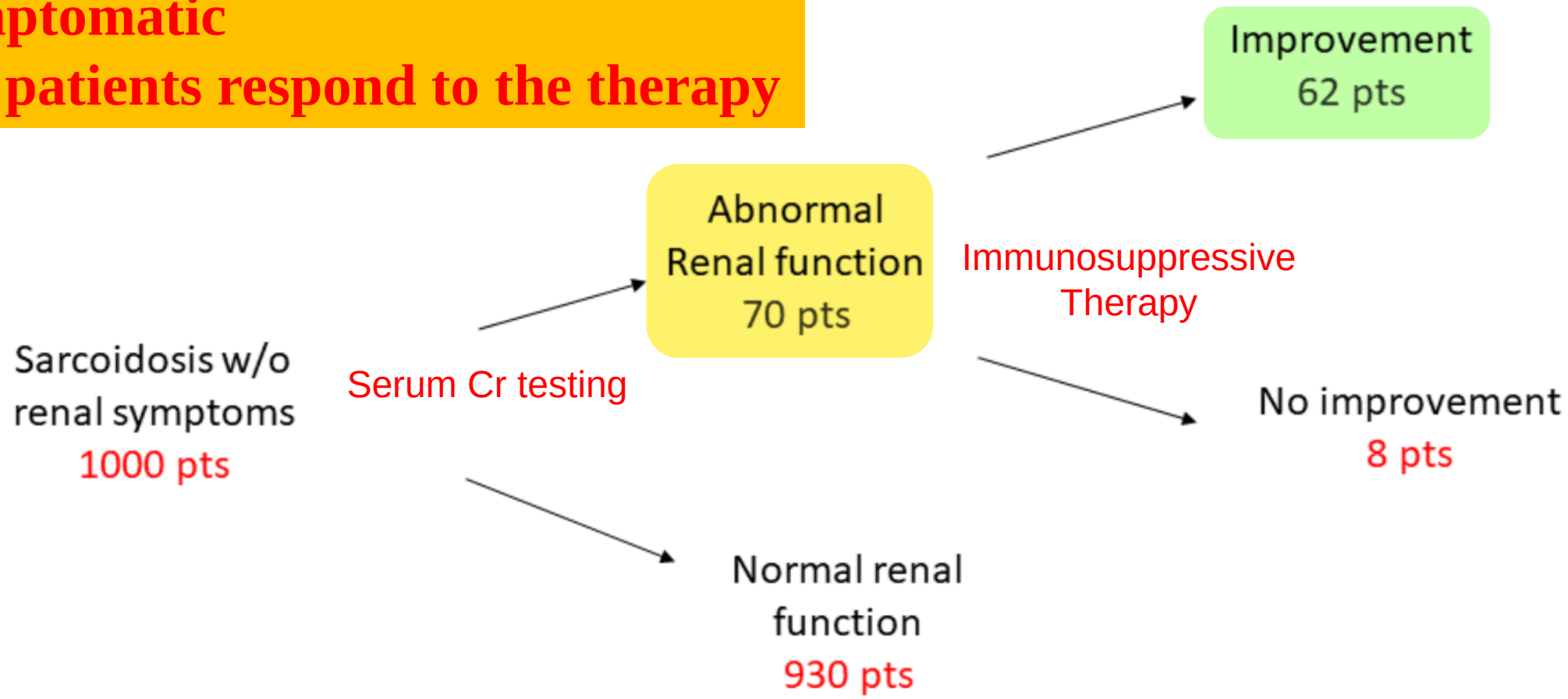
Kidney (1%)

For patients with sarcoidosis who have neither renal symptoms nor established renal sarcoidosis, we suggest baseline serum creatinine testing to screen for renal sarcoidosis (conditional recommendation, very low-quality evidence).

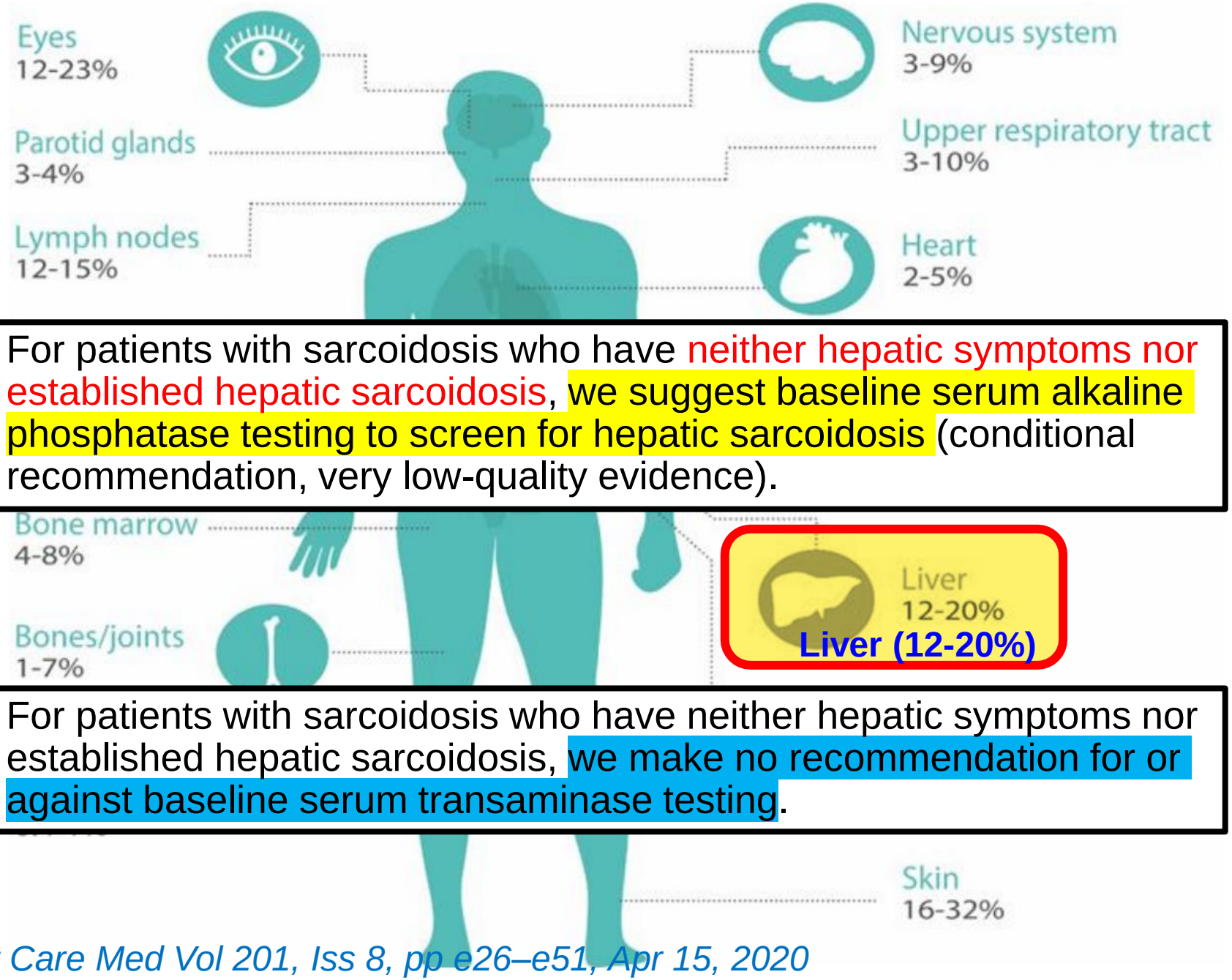
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Screening for Renal Sarcoidosis by Routine Serum Creatinine Testing

Asymptomatic
Most patients respond to the therapy



Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

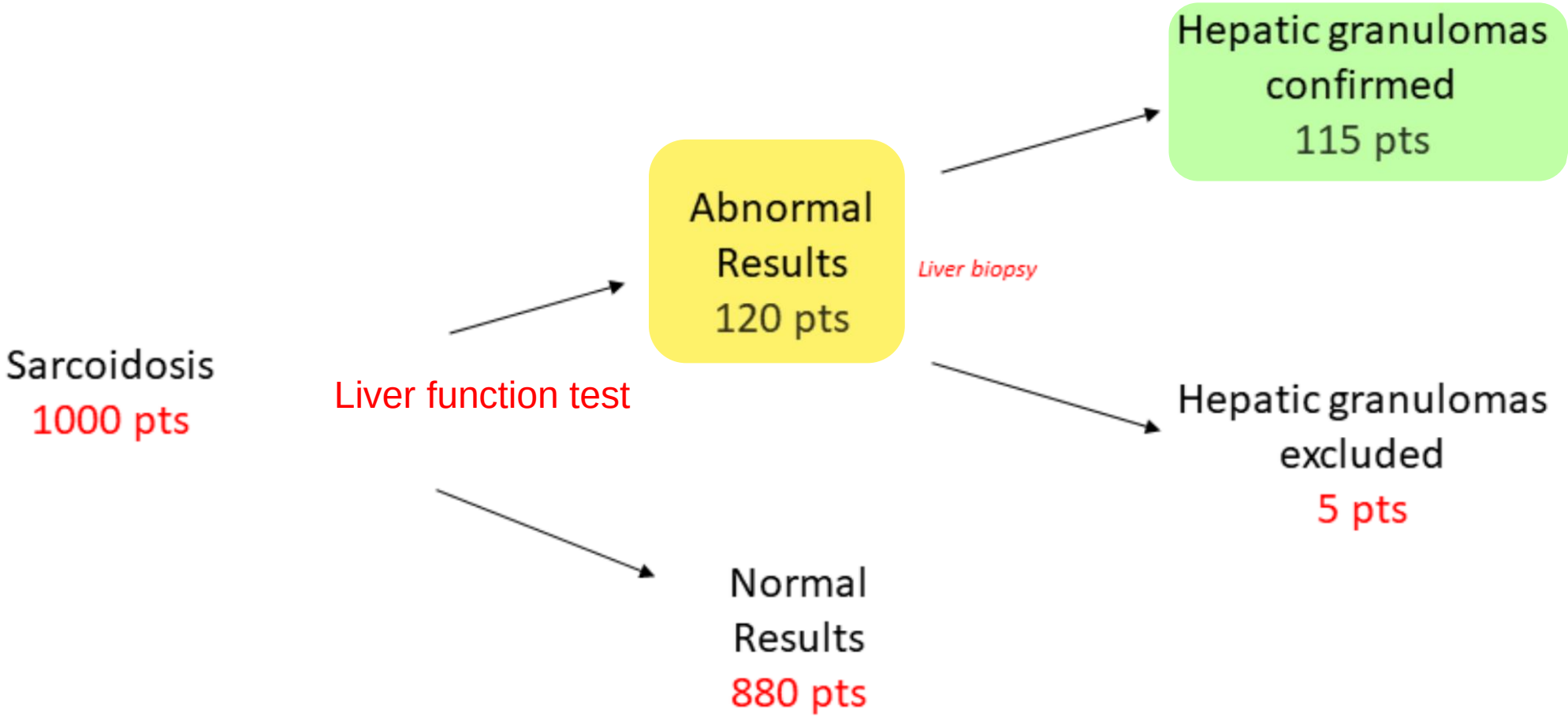


For patients with sarcoidosis who have neither hepatic symptoms nor established hepatic sarcoidosis, we suggest baseline serum alkaline phosphatase testing to screen for hepatic sarcoidosis (conditional recommendation, very low-quality evidence).

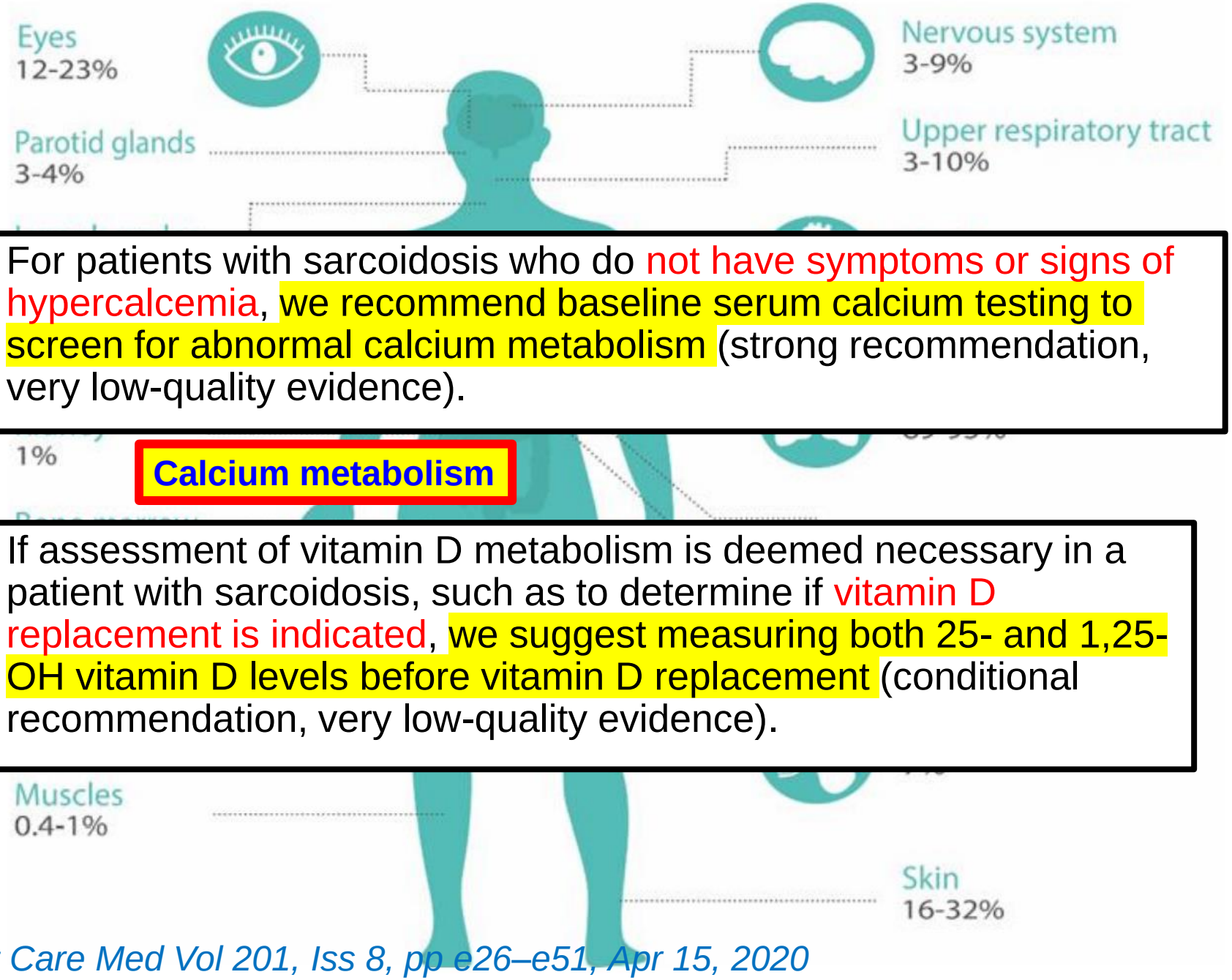
For patients with sarcoidosis who have neither hepatic symptoms nor established hepatic sarcoidosis, we make no recommendation for or against baseline serum transaminase testing.

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Routine Transaminase and Alkaline Phosphatase Testing



Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020



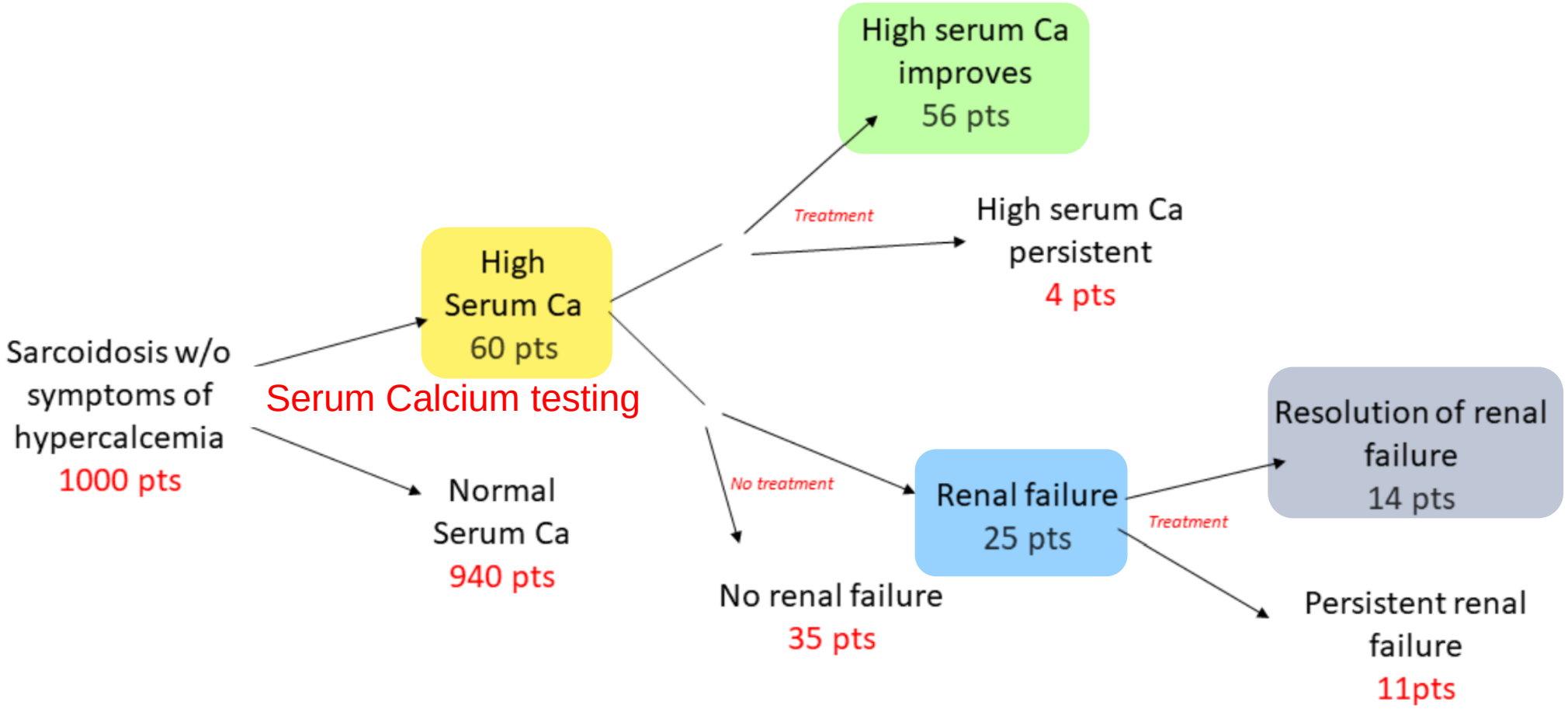
For patients with sarcoidosis who do not have symptoms or signs of hypercalcemia, we recommend baseline serum calcium testing to screen for abnormal calcium metabolism (strong recommendation, very low-quality evidence).

Calcium metabolism

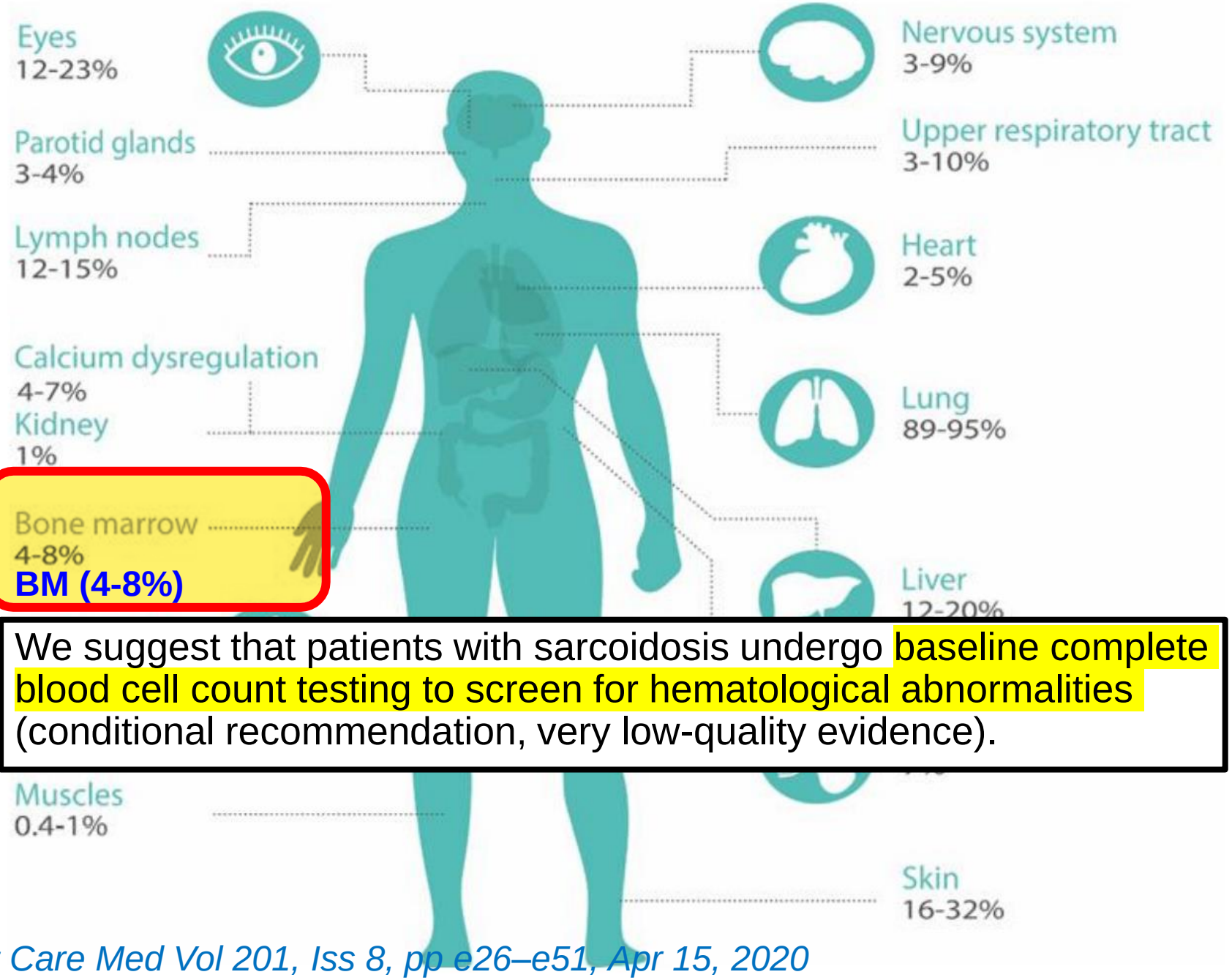
If assessment of vitamin D metabolism is deemed necessary in a patient with sarcoidosis, such as to determine if vitamin D replacement is indicated, we suggest measuring both 25- and 1,25-OH vitamin D levels before vitamin D replacement (conditional recommendation, very low-quality evidence).

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Screening for Abnormal Calcium Metabolism by Routine Serum Calcium and Vitamin D Testing

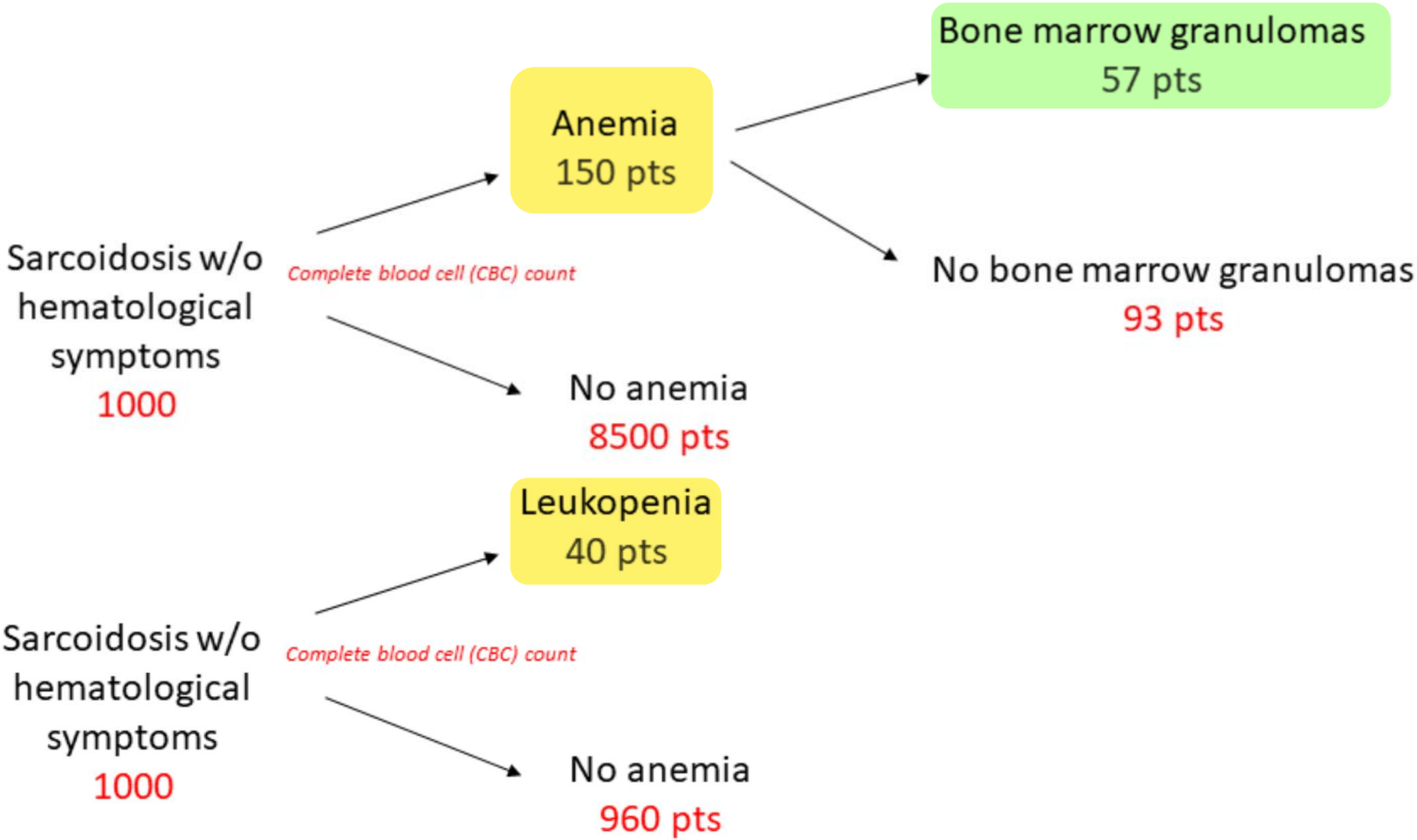


Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

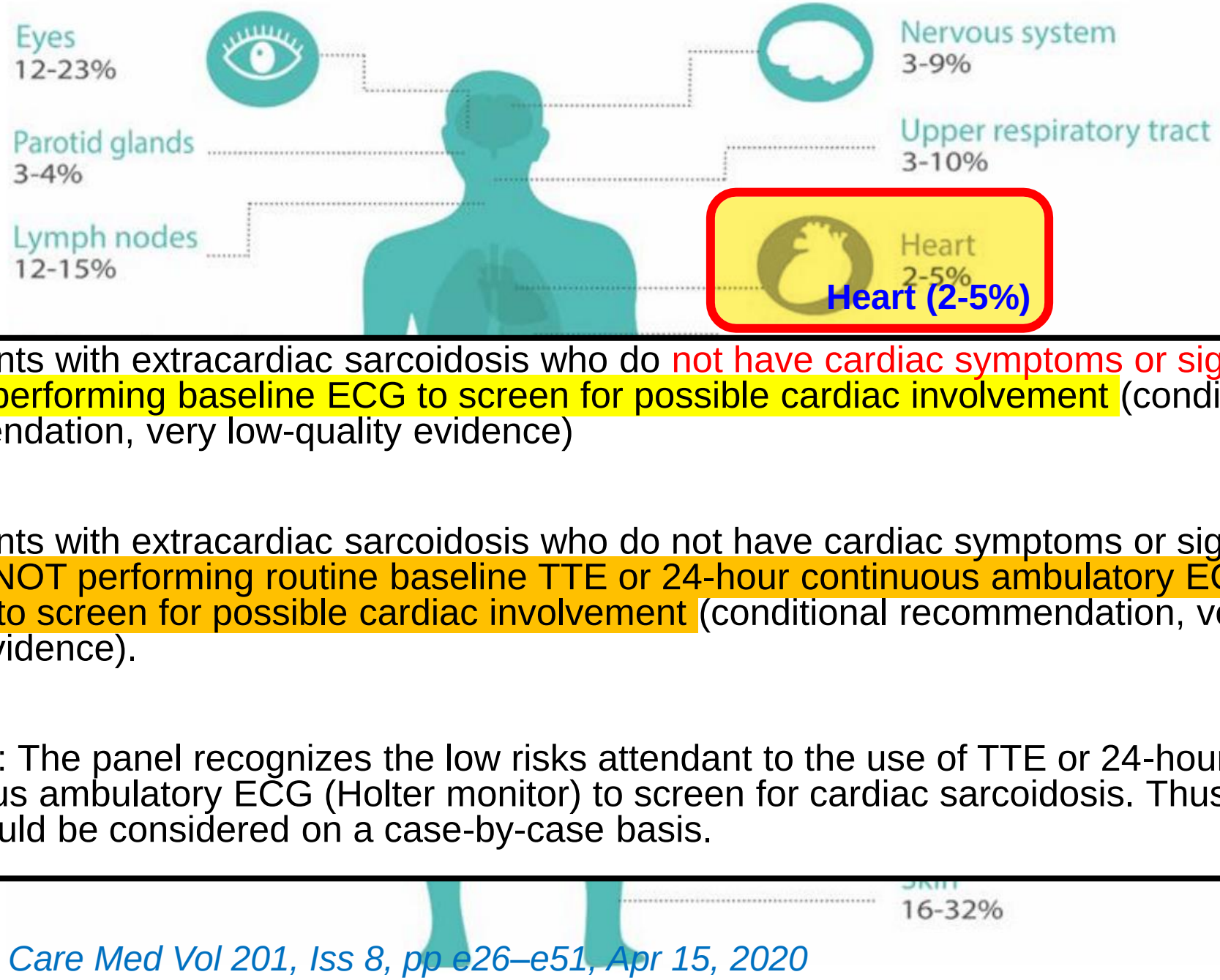


We suggest that patients with sarcoidosis undergo baseline complete blood cell count testing to screen for hematological abnormalities (conditional recommendation, very low-quality evidence).

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020



Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020



- For patients with extracardiac sarcoidosis who do not have cardiac symptoms or signs, we suggest performing baseline ECG to screen for possible cardiac involvement (conditional recommendation, very low-quality evidence)

- For patients with extracardiac sarcoidosis who do not have cardiac symptoms or signs, we suggest NOT performing routine baseline TTE or 24-hour continuous ambulatory ECG (Holter monitor) to screen for possible cardiac involvement (conditional recommendation, very low-quality evidence).

- Remarks: The panel recognizes the low risks attendant to the use of TTE or 24-hour continuous ambulatory ECG (Holter monitor) to screen for cardiac sarcoidosis. Thus, these tests should be considered on a case-by-case basis.

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

	Prevalence in study series
AV block	26%-62%
BBB	12%-61%
SVT	0%-15%
V-Tach	2%-42%
CHF	10%-30%
SD	12%-65%

Am Heart J. 2009 Jan;157(1):9-21.

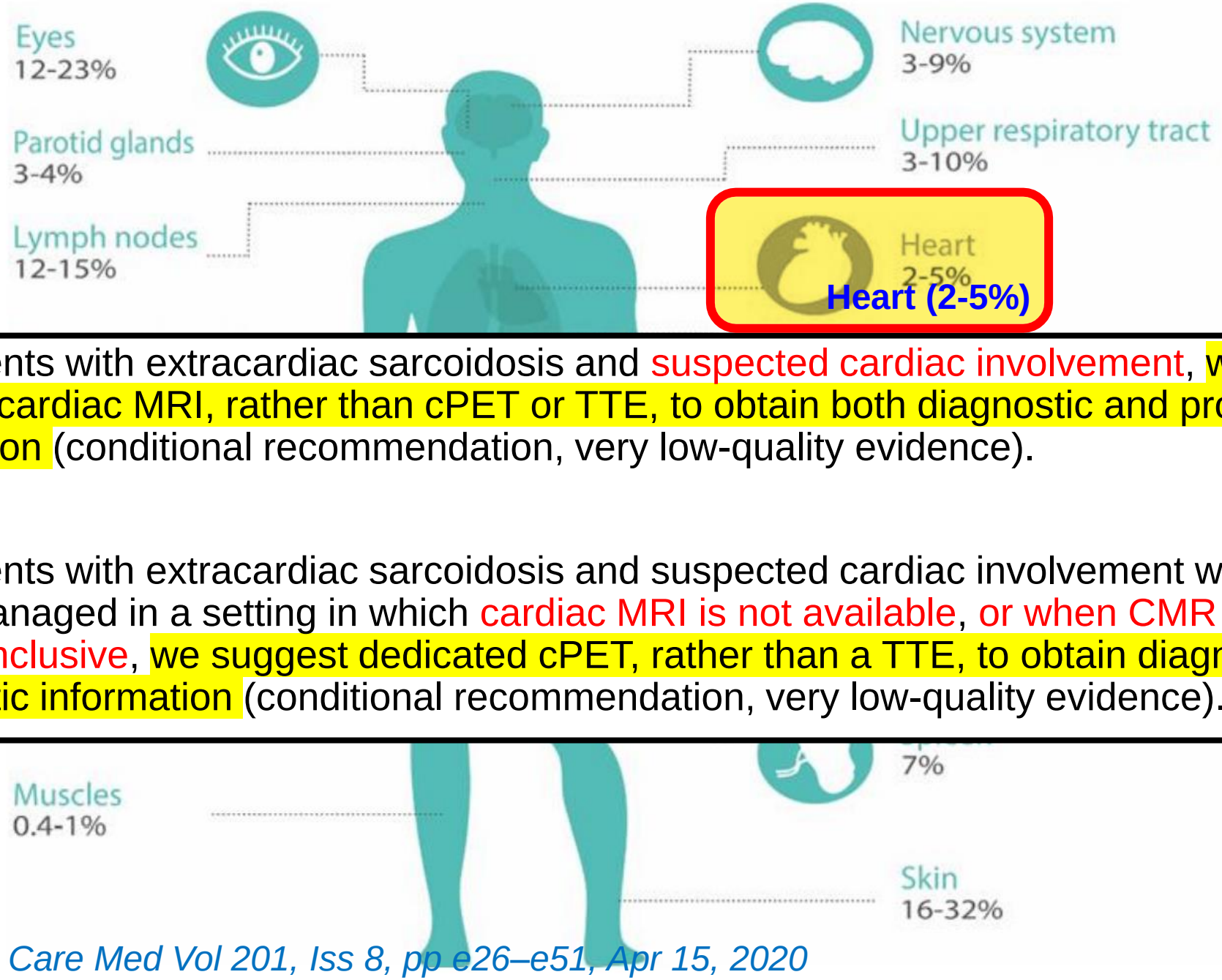
Sensitivity
ECG+TTE: 32%
TTE+Holter: 63%
ECG+Holter: ↓↓

Side-by-side comparisons of diagnostic test characteristics

	ECG	TTE	Holter
Mehta study (only selected study that compared modalities in same population)	Sensitivity= 9%, 95% CI 1-27% Specificity= 97%, 95% CI 86-100%	Sensitivity= 25%, 95% CI 10-47% Specificity= 95%, 95% CI 83-99%	Sensitivity= 50%, 95% CI 29-71% Specificity= 97%, 95% CI 86-100%
Evidence base	2 studies that can't be pooled: Sensitivity= 9%, 95% CI 1-27% Specificity= 97%, 95% CI 86-100% Sensitivity= 92%, 95% CI 62-100% Specificity= 73%, 95% CI 52-88%	1 study Sensitivity= 25%, 95% CI 10-47% Specificity= 97%, 95% CI 86-99%	2 studies Sensitivity= 56%, 95% CI 40-70% Specificity= 95%, 95% CI 87-98%

*One additional study was encountered that evaluated all three modalities in the same population. The study was not selected for our systematic review because it defined an abnormal test based upon any abnormalities, not just those considered important by the JMHW and HRS. This will tend to overestimate the sensitivity and underestimate the specificity. It found the following: ECG- Se 39%, Sp 90%; TTE- Se 70%, Sp 58%; and, Holter- Se 39%, Sp 85%.

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020



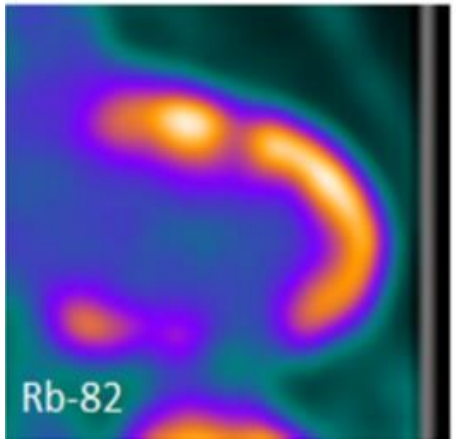
- For patients with extracardiac sarcoidosis and suspected cardiac involvement, we suggest cardiac MRI, rather than cPET or TTE, to obtain both diagnostic and prognostic information (conditional recommendation, very low-quality evidence).

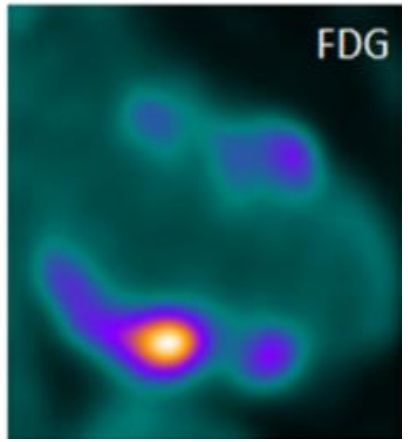
- For patients with extracardiac sarcoidosis and suspected cardiac involvement who are being managed in a setting in which cardiac MRI is not available, or when CMR results are inconclusive, we suggest dedicated cPET, rather than a TTE, to obtain diagnostic and prognostic information (conditional recommendation, very low-quality evidence).

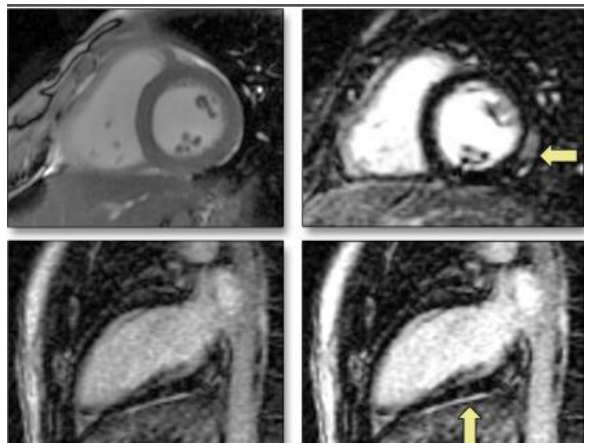
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Comparison

	② PET	① cMRI	TTE
Reference standard	JMHW criteria	JMHW criteria	+MRI or +PET
Diagnosis of cardiac sarcoidosis	Sensitivity 70% (95 CI 60-78%) Specificity 78% (95% CI 71-84%) PPV 69% (95% CI 60-77%) NPV 79% (95% CI 72-85%)	Sensitivity 82% (95 CI 72-89%) Specificity 73% (95% CI 67-79%) PPV 58% (95% CI 49-67%) NPV 90% (95% CI 84-94%)	Sensitivity 25%, 95% CI 10-47% Specificity 97%, 95% CI 86-99% PPV 75%, 95% CI 41-93% NPV 67%, 95% CI 53-78%







Late Gadolinium Enhancement

cMRI>cPET
Prognotic capability ↑
Cost ↓
False-positive ↓

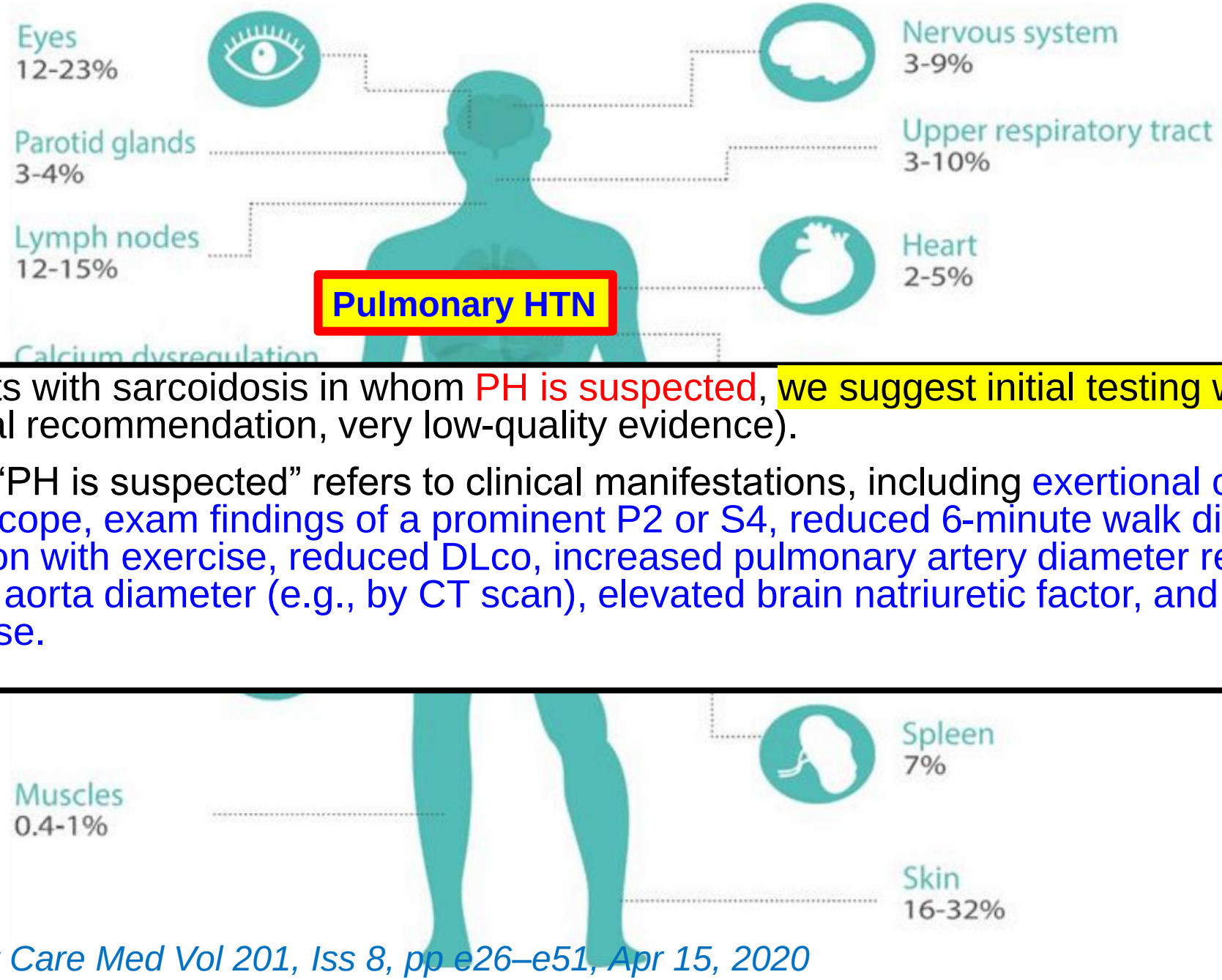
Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

BTS guideline

- Cardiac sarcoidosis and/or pulmonary hypertension should be considered in all patients with pulmonary sarcoidosis who have levels of breathlessness which are disproportionate to their lung function impairment.

- Baseline testing in all patients with suspected cardiac sarcoidosis (ie, those with ECG abnormalities, cardiac symptoms or breathlessness out of context with their pulmonary function) should include an ECG and echocardiogram. Abnormalities in ECG or echocardiogram which suggest cardiac sarcoidosis should be confirmed with CMR or PET.

Thillai M, et al. Thorax 2020;0:1–17.

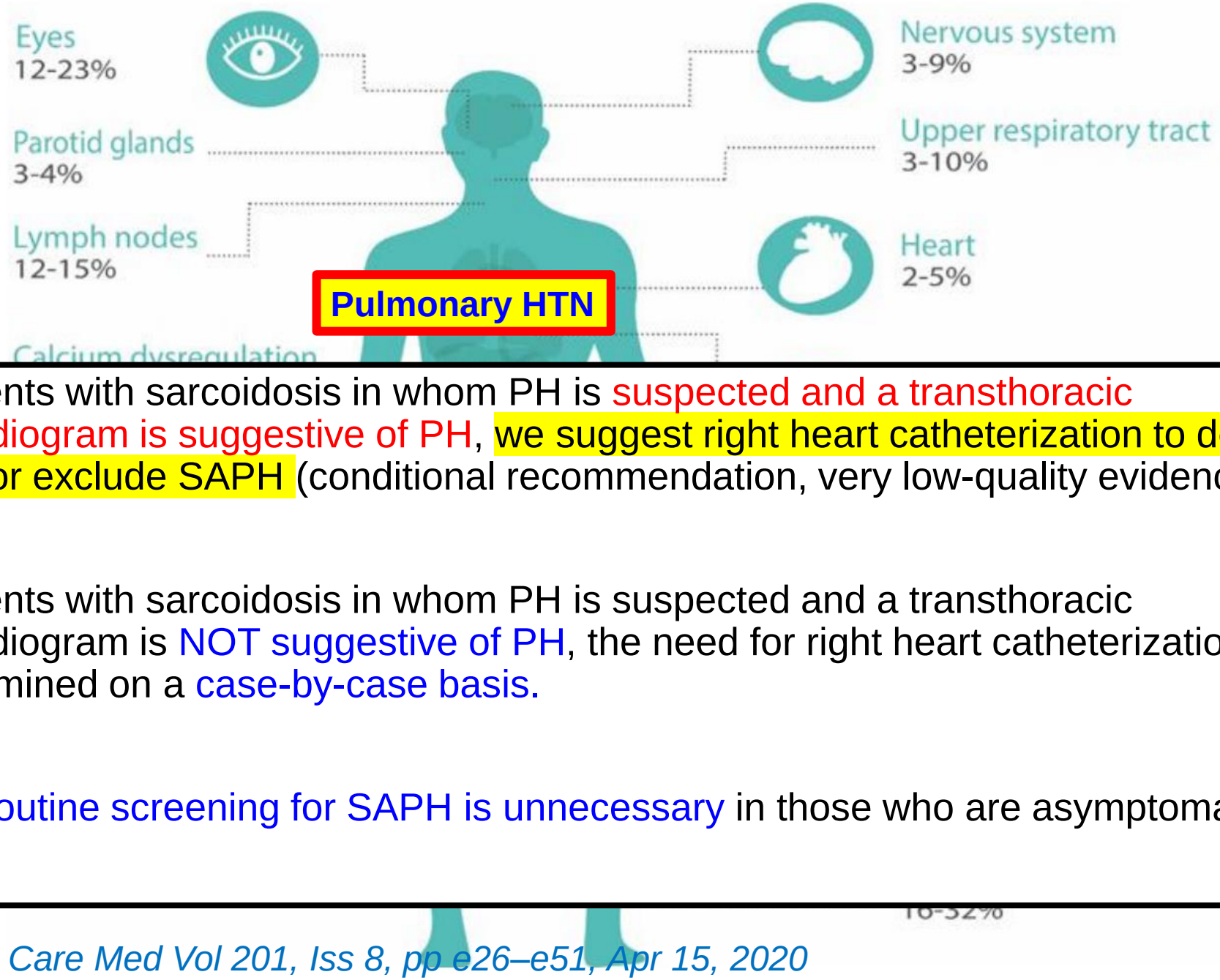


Pulmonary HTN

For patients with sarcoidosis in whom PH is suspected, we suggest initial testing with TTE (conditional recommendation, very low-quality evidence).

Remarks: “PH is suspected” refers to clinical manifestations, including exertional chest pain and/or syncope, exam findings of a prominent P2 or S4, reduced 6-minute walk distance, desaturation with exercise, reduced DLco, increased pulmonary artery diameter relative to ascending aorta diameter (e.g., by CT scan), elevated brain natriuretic factor, and fibrotic lung disease.

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

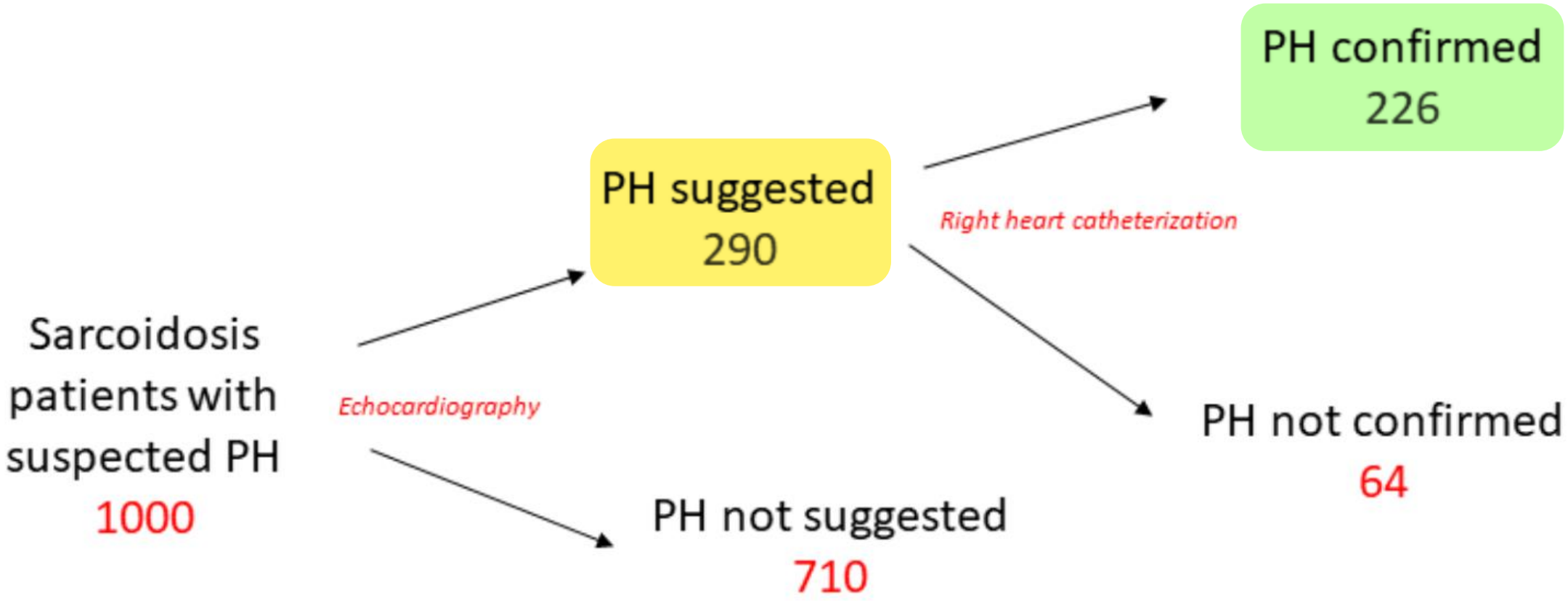


- For patients with sarcoidosis in whom PH is suspected and a transthoracic echocardiogram is suggestive of PH, we suggest right heart catheterization to definitively confirm or exclude SAPH (conditional recommendation, very low-quality evidence).

- For patients with sarcoidosis in whom PH is suspected and a transthoracic echocardiogram is NOT suggestive of PH, the need for right heart catheterization should be determined on a case-by-case basis.

- Finally, routine screening for SAPH is unnecessary in those who are asymptomatic

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

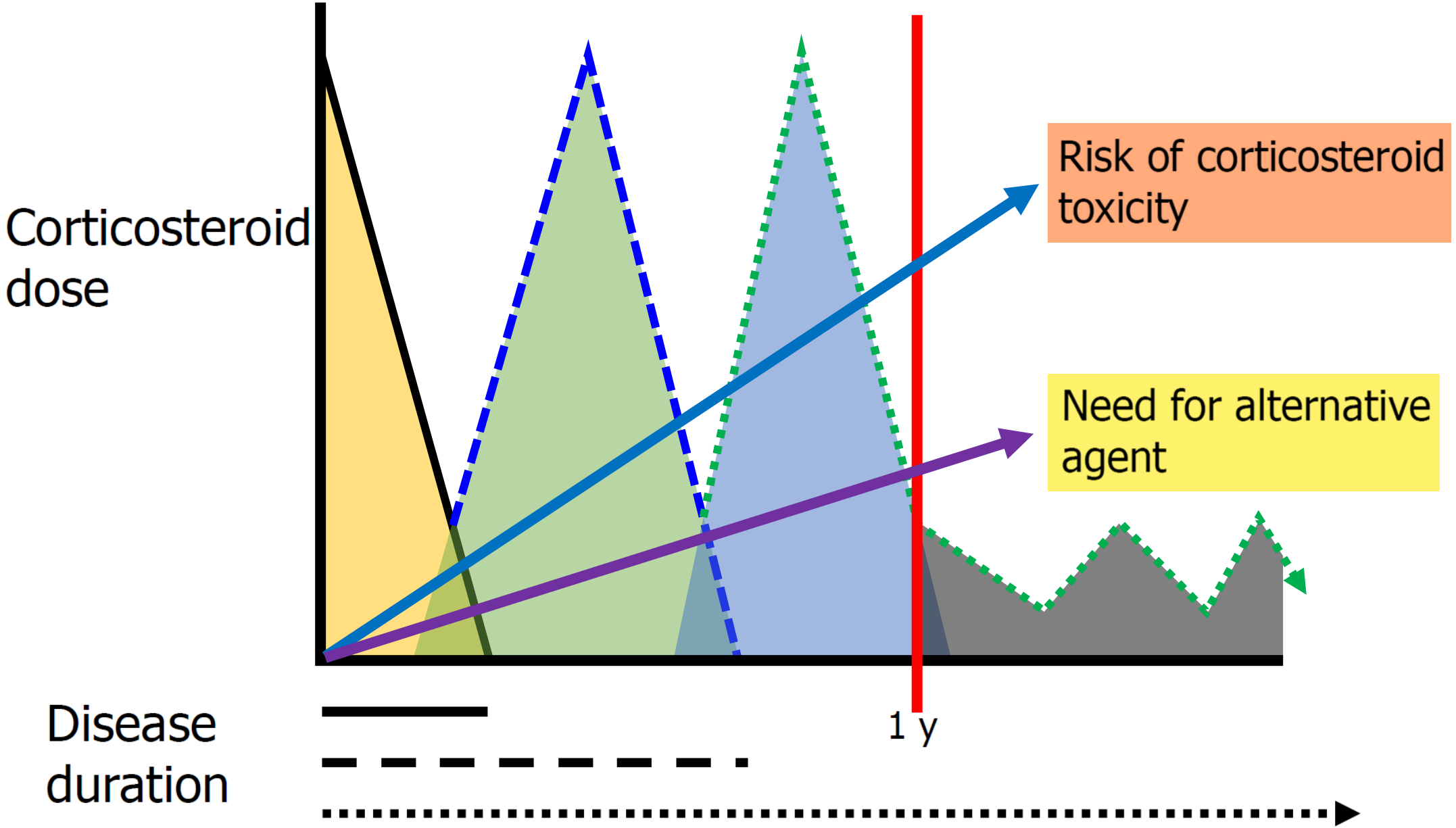


Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020

Table 5. Best Practice Recommendations for Detection of Delayed Onset of Extrapulmonary Sarcoidosis Manifestations after Negative Baseline Screening

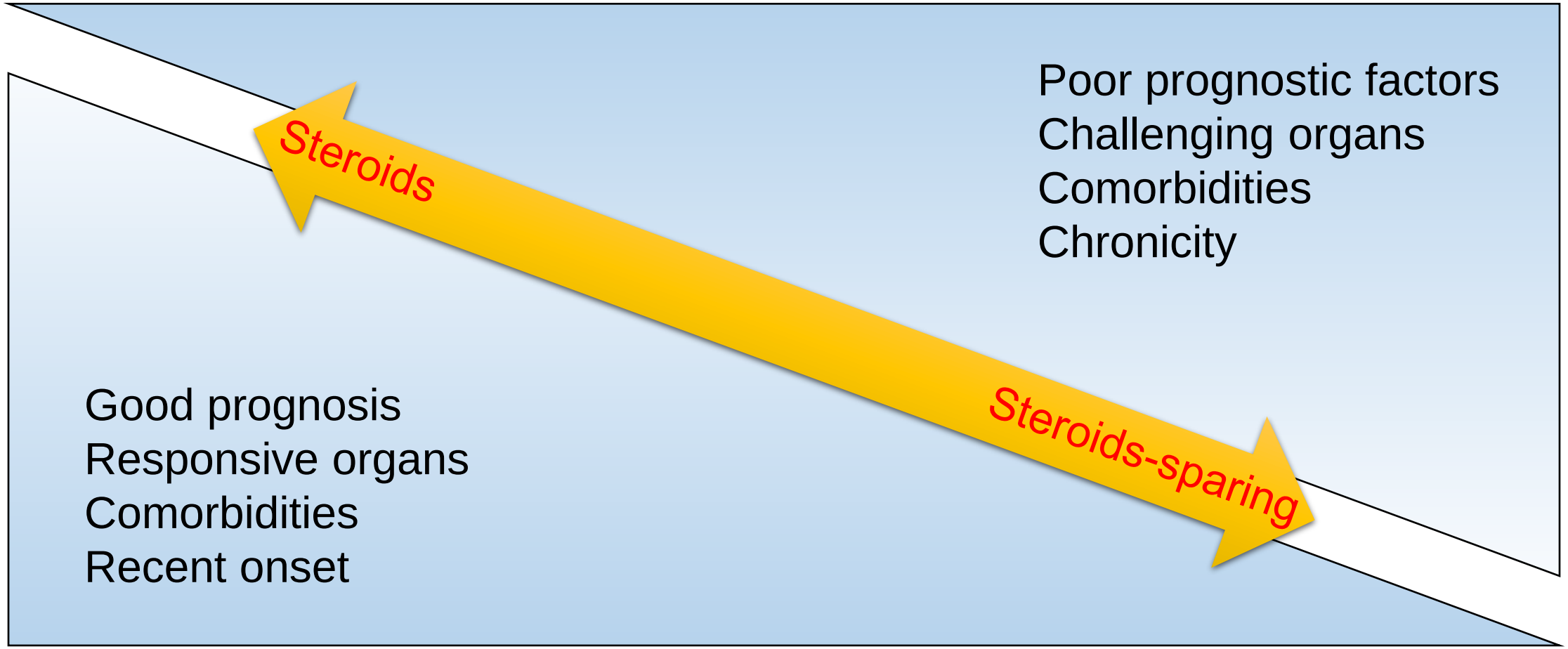
Test Parameter	Routine Testing for New Sarcoidosis Involvement	New Conditions Triggering a Specific Testing for Extrapulmonary Sarcoidosis Involvement
Calcium	Annually	Kidney stones Acute or acute on chronic renal failure
Creatinine	Annually	—
Alkaline phosphatase	Annually	—
Eye exam	None	Change in vision • Floaters • Blurry • Visual field loss Eye pain, photophobia, or redness (sustained)
Cardiac testing (*see* Questions 9)	None	Chest pains Palpitations Near syncope/syncope Sustained bradycardia or tachycardia Dyspnea out of proportion to lung disease New ECG findings
Pulmonary hypertension testing (*see* Question 10)	None	Clinical signs of pulmonary hypertension (*see* main text)

Am J Respir Crit Care Med Vol 201, Iss 8, pp e26–e51, Apr 15, 2020



Rheum Dis Clin North Am. 2016 Feb;42(1):119-35

Corticosteroid



Clin Chest Med. 2015 Dec;36(4):751-67

REVIEW
PULMONARY SARCOIDOSIS

Clinical phenotyping: role in treatment decisions in sarcoidosis

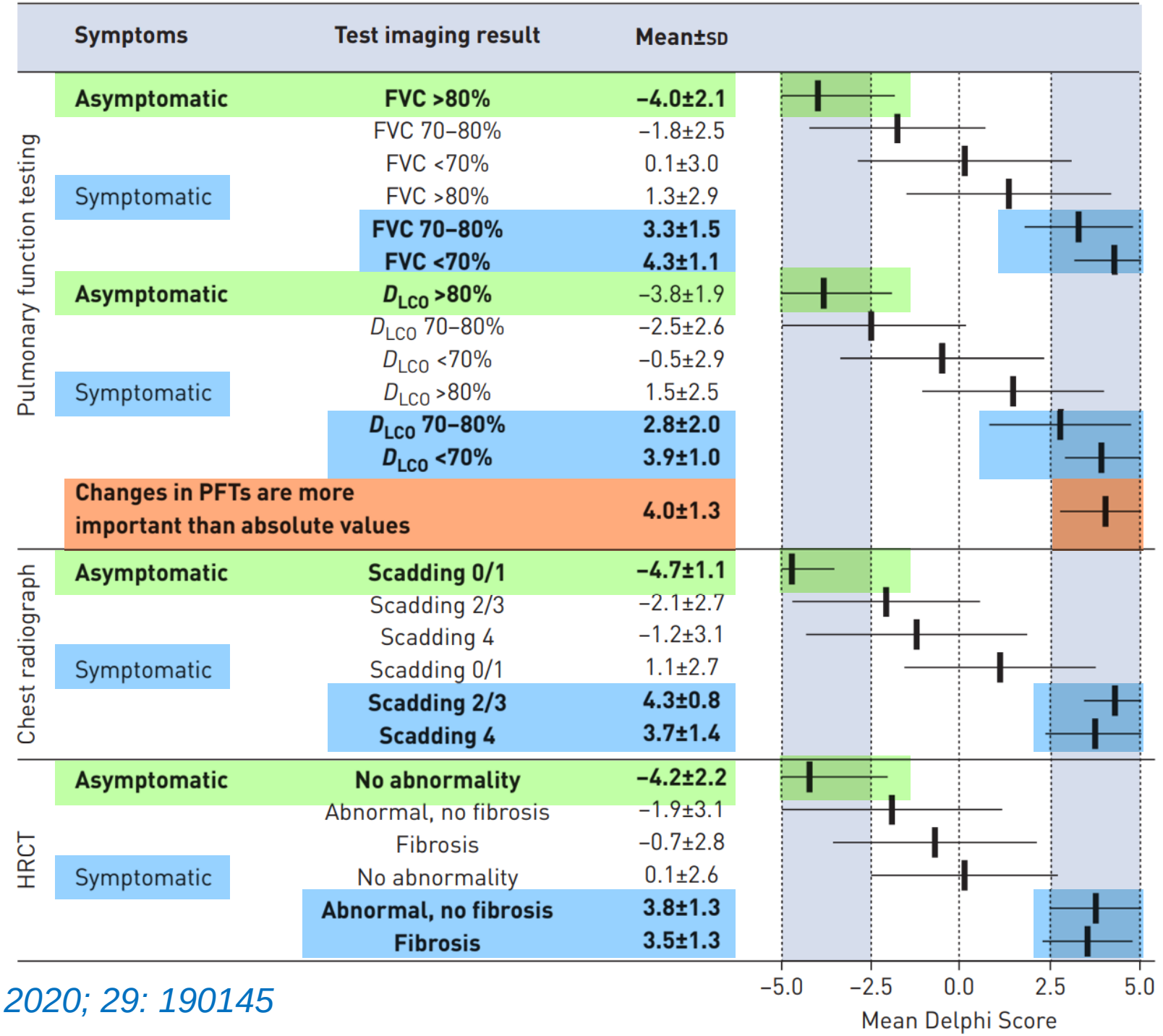
Robert P. Baughman[1], Mary Beth Scholand[2] and Franck F. Rahaghi[3]

N=26

폐기능검사

Stage

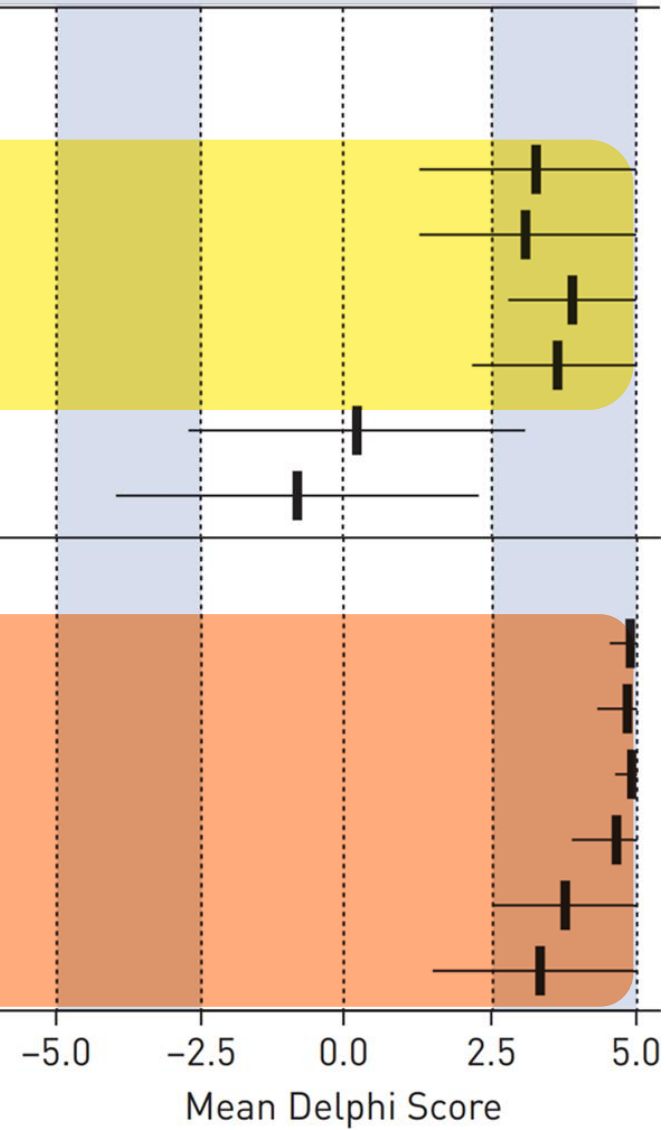
Fibrosis



Eur Respir Rev 2020; 29: 190145

Delphi consensus on the role of extrapulmonary disease in treatment decisions

Symptoms	Mean±SD
Patients should be treated if:	
Asymptomatic	
Cardiac involvement	**3.3±2.1**
Neurologic involvement	**3.1±1.8**
Ocular involvement	**3.9±1.1**
Renal involvement	**3.6±1.5**
Cutaneous involvement	**0.2±2.9**
Hepatic involvement	**−0.9±3.1**
Symptomatic	
Cardiac involvement	**4.9±0.4**
Neurologic involvement	**4.8±0.5**
Ocular involvement	**4.9±0.3**
Renal involvement	**4.6±0.8**
Cutaneous involvement	**3.7±1.2**
Hepatic involvement	**3.3±1.8**



Eur Respir Rev 2020; 29: 190145

Delphi consensus recommendations for a treatment algorithm in pulmonary sarcoidosis

Lesley Ann Saketkoo[3], urinder S. Birring[6], Ulrich Costabel[7], K. Gerke[10], Jan C. Grutters[9], nis James IV[12], Sanjay Kalra[13], E. Lower[2], Lisa A. Maier[16], eim[18], Eva M. Carmona Porquera[13], nd Mary Beth Scholand[21]

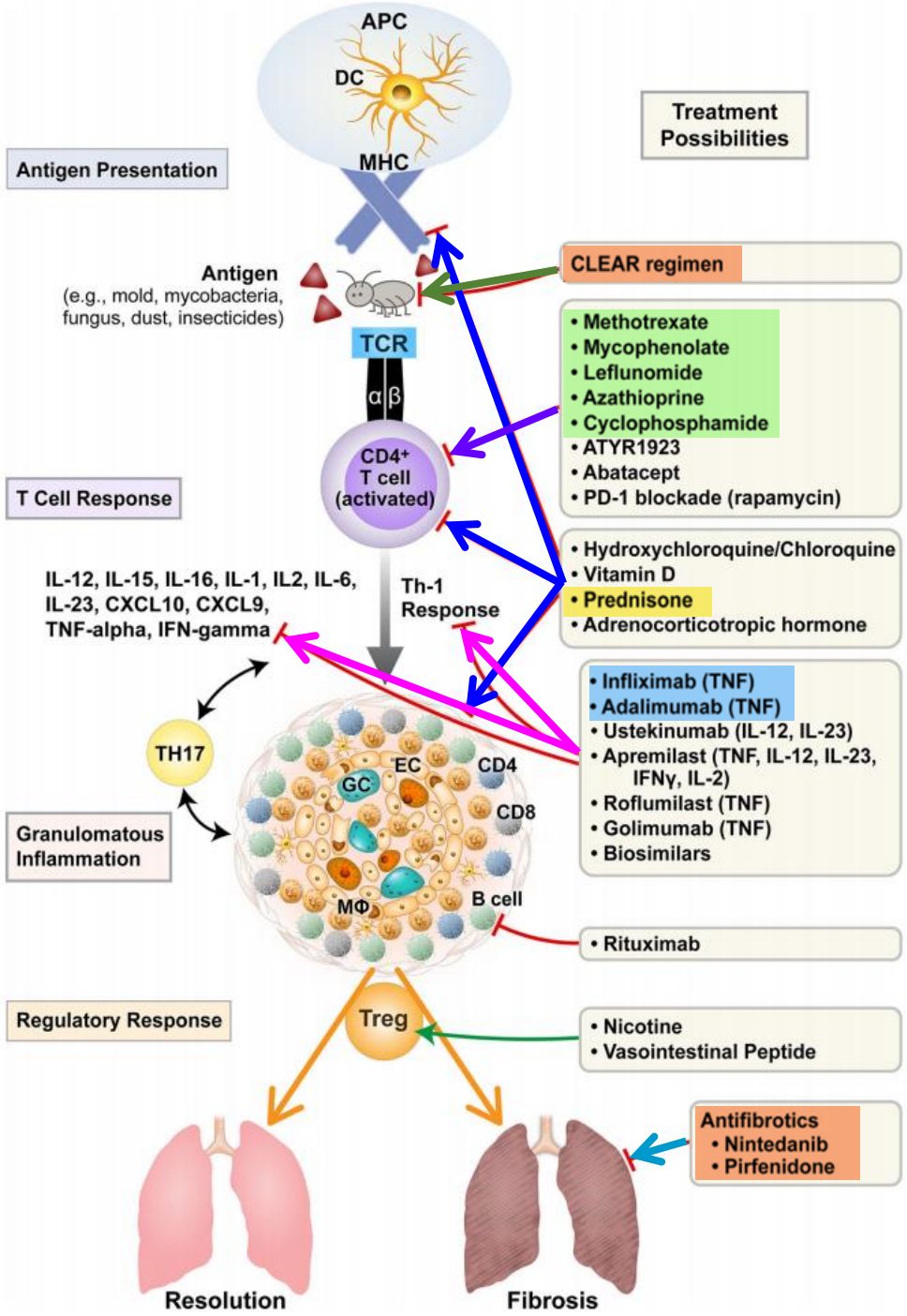
TABLE 1 Characteristics of the Delphi panellists

N=26

Characteristic	Panellists n
Specialty#	
Pulmonology	19
Critical care	3
Rheumatology	2
Cardiology	1
Oncology	1
Experience treating sarcoidosis¶	
6–10 years	5
11–20 years	8
>20 years	8
Patients with sarcoidosis treated in entire career¶	
⩽500	7
501–1000	8
1001–3000	3
>3000	2
Patients with sarcoidosis treated last year¶	
⩽50	7
51–100	8
101–300	3
>300	2

#: highest degree of specialty is reported; ¶: some panellists did not respond to these questions.

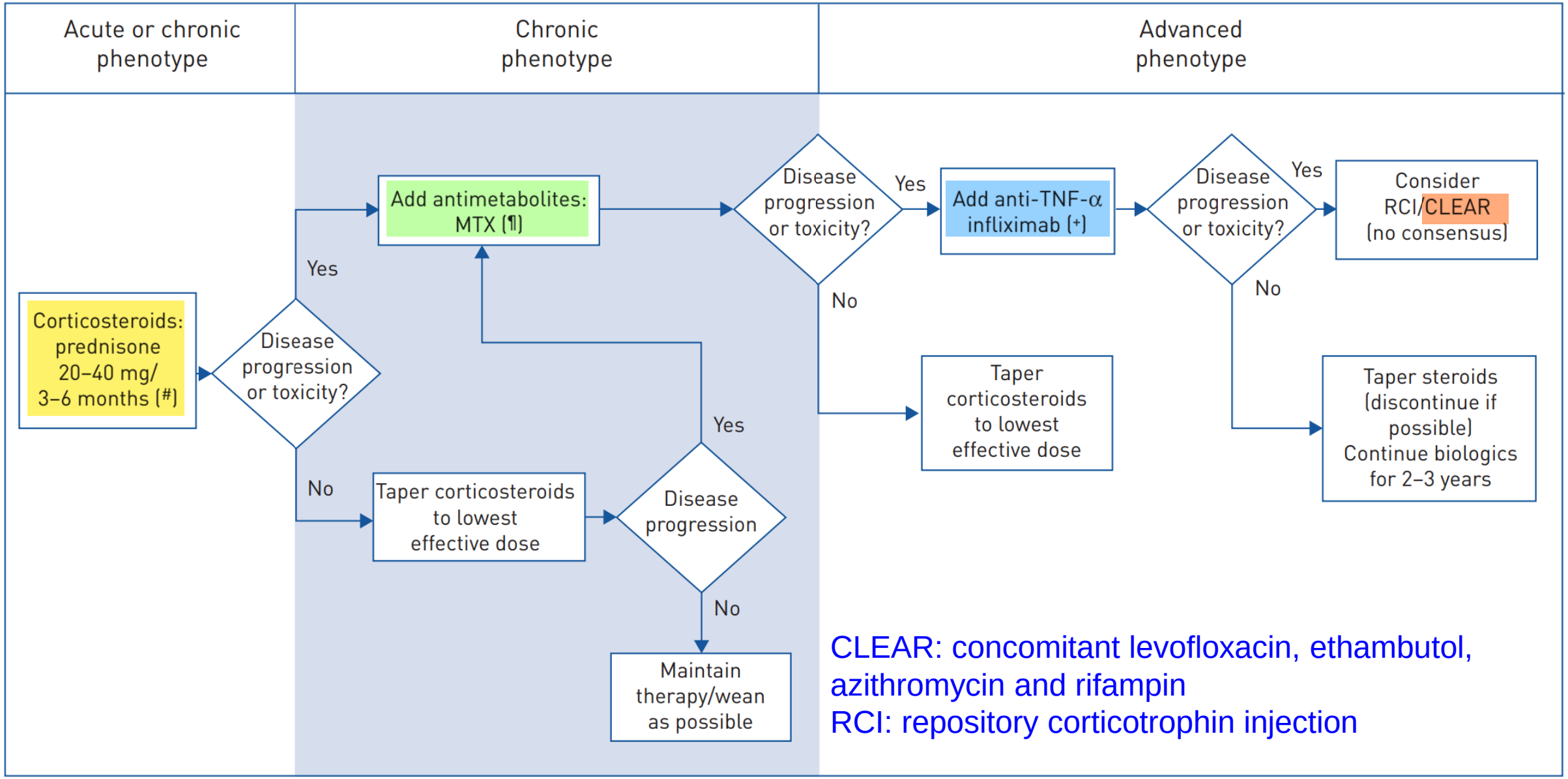
Eur Respir Rev 2020; 29: 190146



	Drug name	Suggested dose range
First-Line Agents	Corticosteroids (Prednisone)	20–40 mg/day initial Dose, tapered to 7.5–15 mg/day
Second-Line Agents	Methotrexate	7.5–25 mg/week orally or subcutaneously
	Hydroxychloroquine	200–400 mg/day
	Leflunomide	10–20 mg/day
	Azathioprine	50–200 mg/day
	Mycophenolate	500–3,000 mg/day
Third-Line Agents	Infliximab	3–5 mg/kg intravenously at weeks 0, 2, and every 4–8 weeks thereafter
	Adalimumab	40 mg subcutaneous every 1–2 weeks

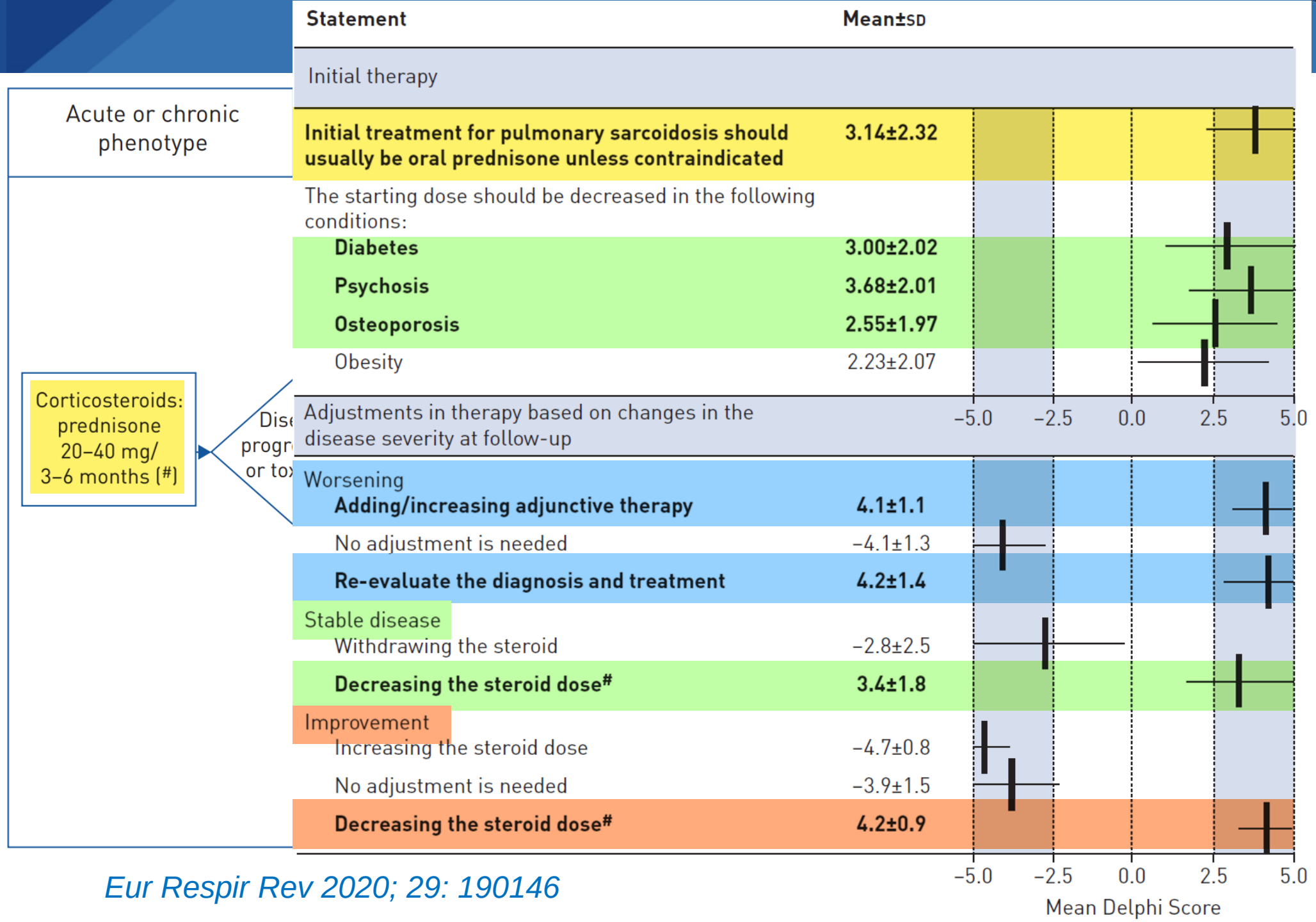
Front. Immunol. 11:545413.2020

Treatment algorithm for symptomatic or organ-threatening sarcoidosis



CLEAR: concomitant levofloxacin, ethambutol, azithromycin and rifampin
RCI: repository corticotrophin injection

Eur Respir Rev 2020; 29: 190146



Eur Respir Rev 2020; 29: 190146

BTS Clinical Statement on pulmonary sarcoidosis

Management

1. There is often a fine line to making the decision to start pharmacological treatment and all patients should be fully informed and be at the heart of this decision-making process.
2. While there is no good evidence for any drug regimen in sarcoidosis, the majority of patients needing treatment should initially be treated with steroids ranging from 10 mg of prednisolone per day in long-standing and insidiously progressive disease, up to 20 to 40 mg per day in more acute disease. A maintenance dose of 5 to 10 mg after these initial doses for 6 to 12 months is usual.
3. Most patients who need treatment should be offered methotrexate (administered orally, or subcutaneously) as the first choice of second-line agent.
4. Referral for lung transplantation should be considered in all patients with advanced pulmonary fibrosis and associated pulmonary hypertension.
5. All patients with sarcoidosis-related fatigue should have a systematic approach to diagnosis of the cause of fatigue and management initiated as appropriate.
6. In line with other chronic lung conditions, patients should be offered smoking cessation advice and support for anxiety or depression if needed.

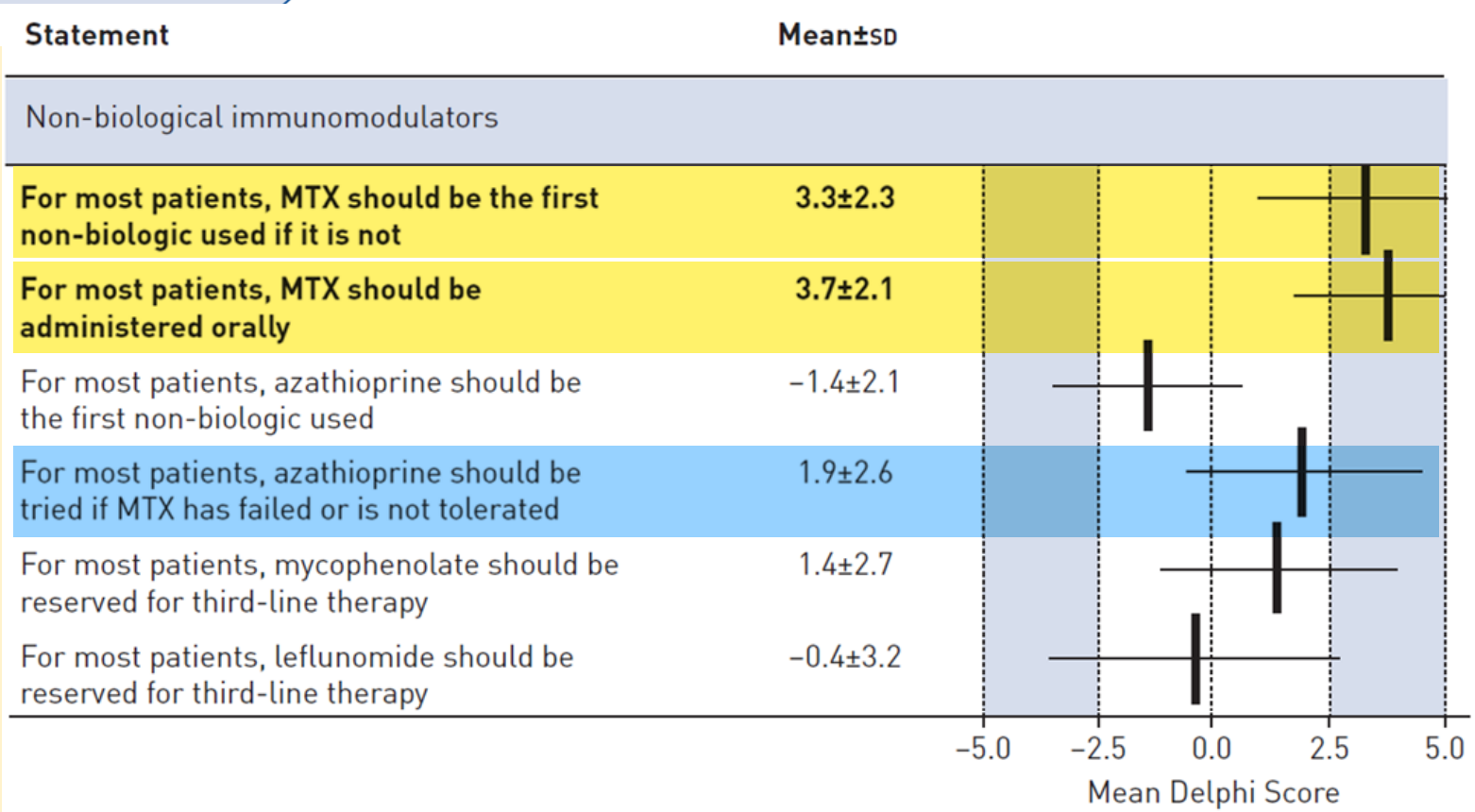
Thillai M, et al. Thorax 2020;0:1–17.

Acute or chronic phenotype	Chronic phenotype

1. Progression of pulmonary disease or an unacceptable symptom burden despite adequate steroid therapy.
2. Intolerable steroid side effects.
3. Inability to taper steroid below 10 to 15 mg per day.
4. The presence of major comorbidities likely to be adversely affected by steroid therapy (severe obesity, DM, osteoporosis, HTN).
5. A strong patient aversion to the use of steroids, in which case, a second-line agent may occasionally be used as initial therapy.

BTS guideline

as possible



Eur Respir Rev 2020; 29: 190146

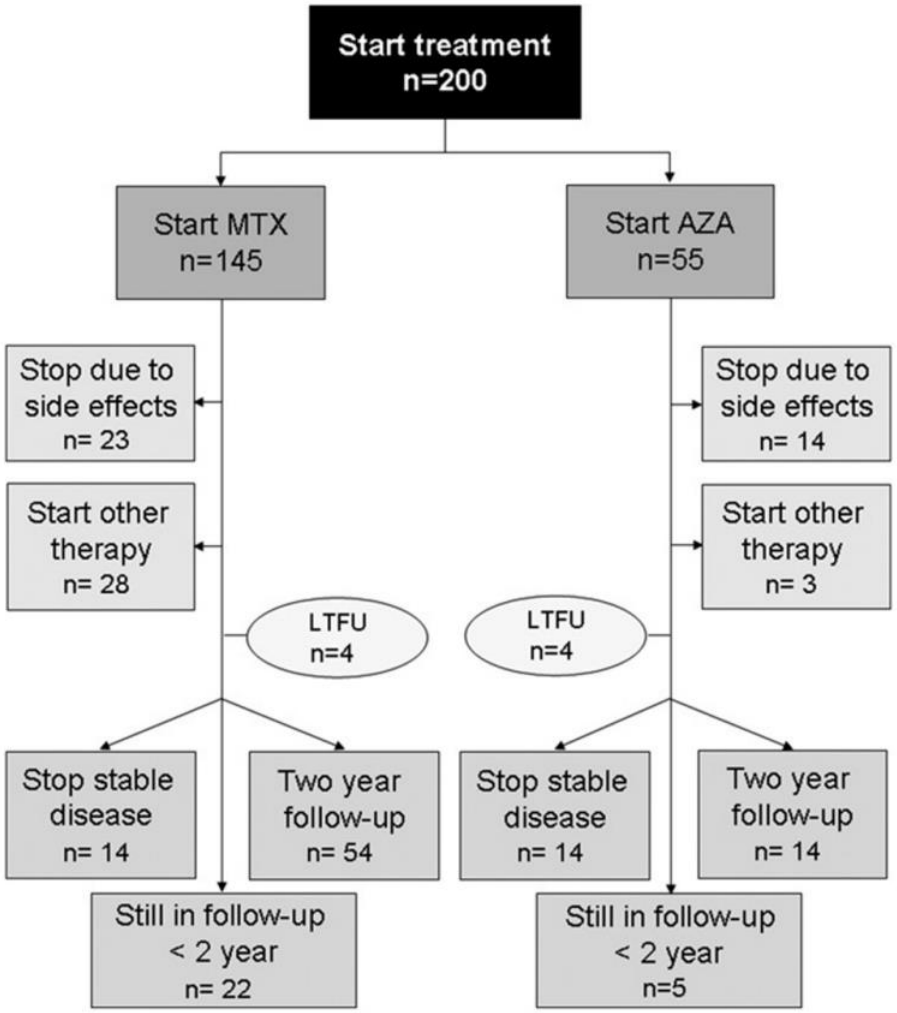
BTS Clinical Statement on pulmonary sarcoidosis

Management

1. There is often a fine line to making the decision to start pharmacological treatment and all patients should be fully informed and be at the heart of this decision-making process.
2. While there is no good evidence for any drug regimen in sarcoidosis, the majority of patients needing treatment should initially be treated with steroids ranging from 10 mg of prednisolone per day in long-standing and insidiously progressive disease, up to 20 to 40 mg per day in more acute disease. A maintenance dose of 5 to 10 mg after these initial doses for 6 to 12 months is usual.
3. Most patients who need treatment should be offered methotrexate (administered orally, or subcutaneously) as the first choice of second-line agent.
4. Referral for lung transplantation should be considered in all patients with advanced pulmonary fibrosis and associated pulmonary hypertension.
5. All patients with sarcoidosis-related fatigue should have a systematic approach to diagnosis of the cause of fatigue and management initiated as appropriate.
6. In line with other chronic lung conditions, patients should be offered smoking cessation advice and support for anxiety or depression if needed.

Thillai M, et al. Thorax 2020;0:1–17.

Azathioprine vs Methotrexate

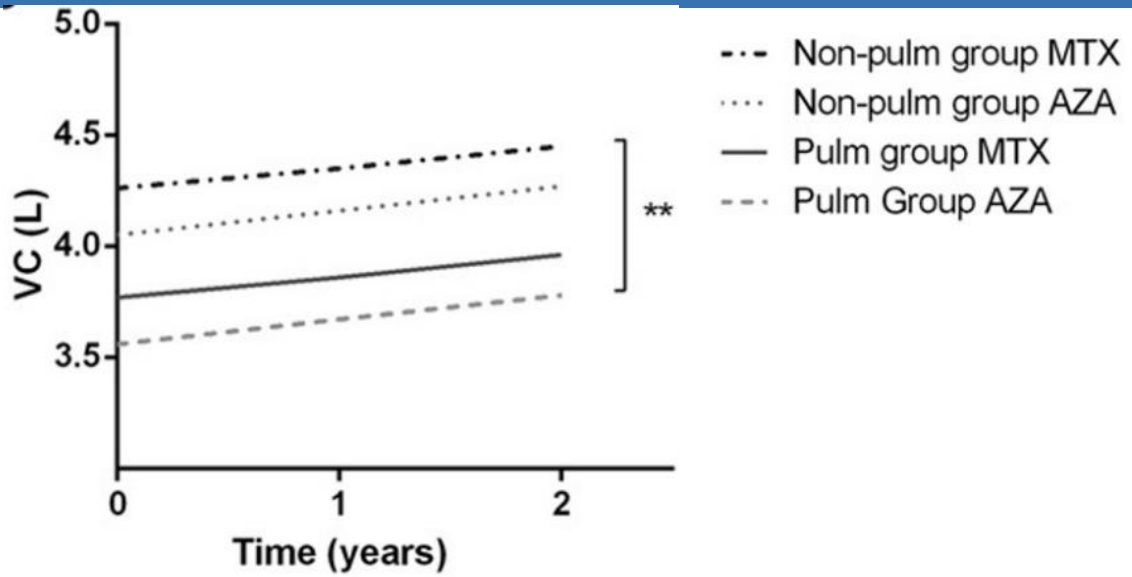


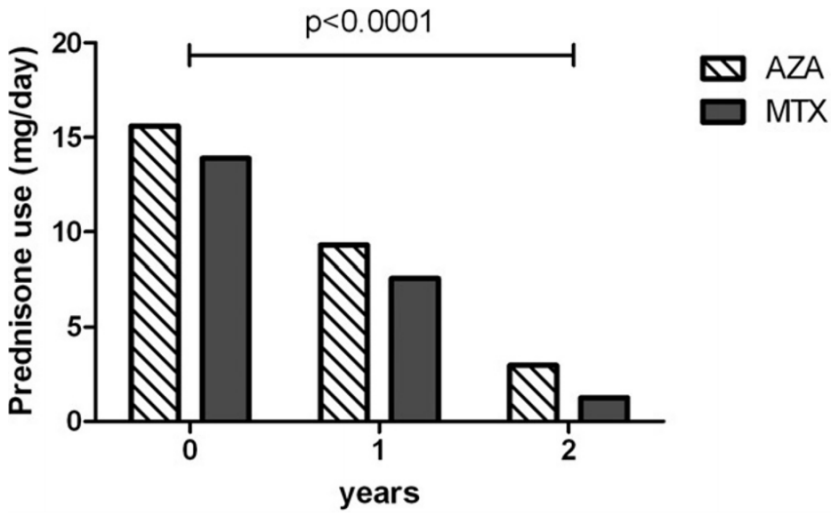
- Retrospective cohort study, 1yr
- Similar in
  - Improving lung function
  - Prednisone dose reduction
  - Benefit on extrapulmonary disease
- Infection: AZA>MTX

  (34.6% vs. 18.1%, p=0.01)

CHEST 2013; 144(3):805–812

Azathioprine vs Methotrexate



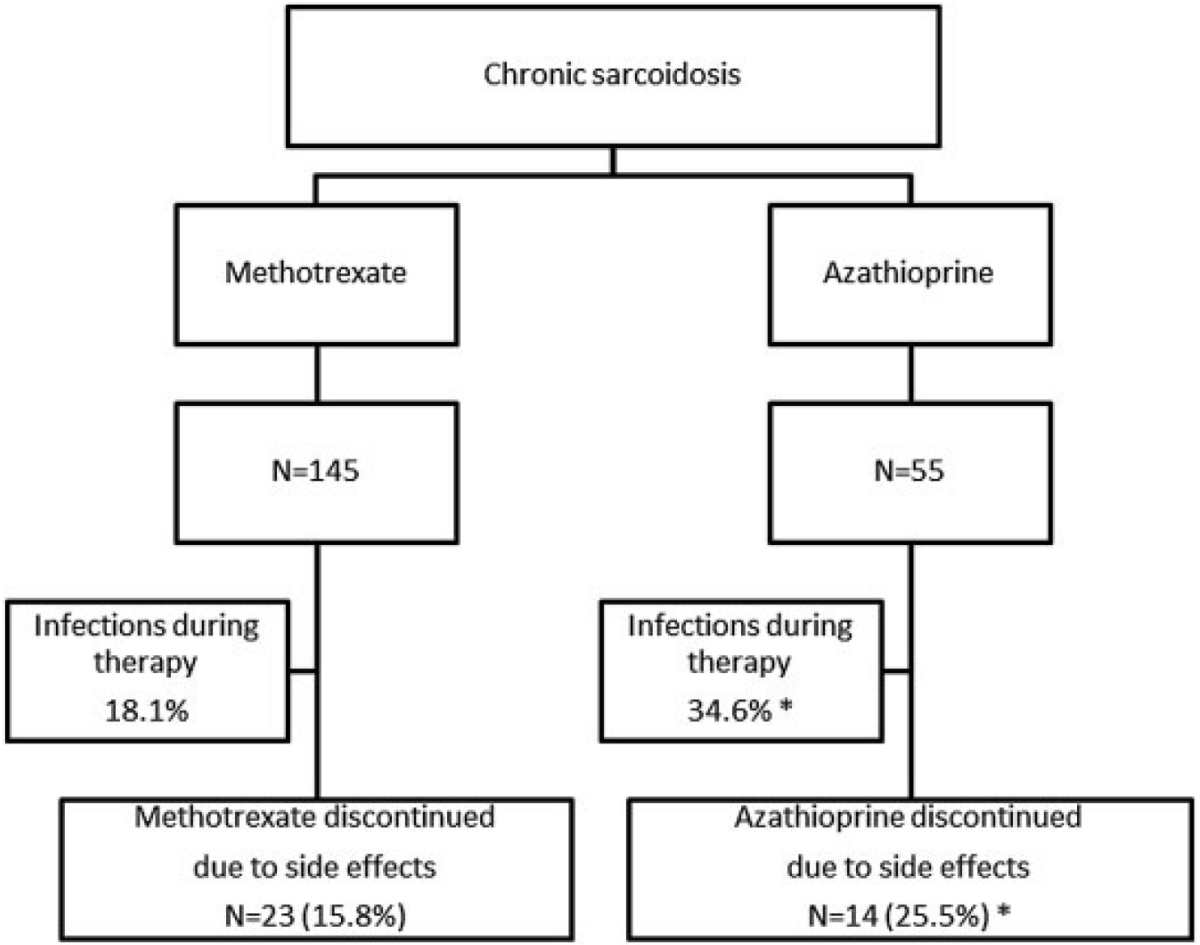


- Retrospective cohort study, 1yr
- Similar in
  - Improving lung function
  - Prednisone dose reduction
  - Benefit on extrapulmonary disease
- Infection: AZA>MTX

  (34.6% vs. 18.1%, p=0.01)

CHEST 2013; 144(3):805–812

Azathioprine vs Methotrexate

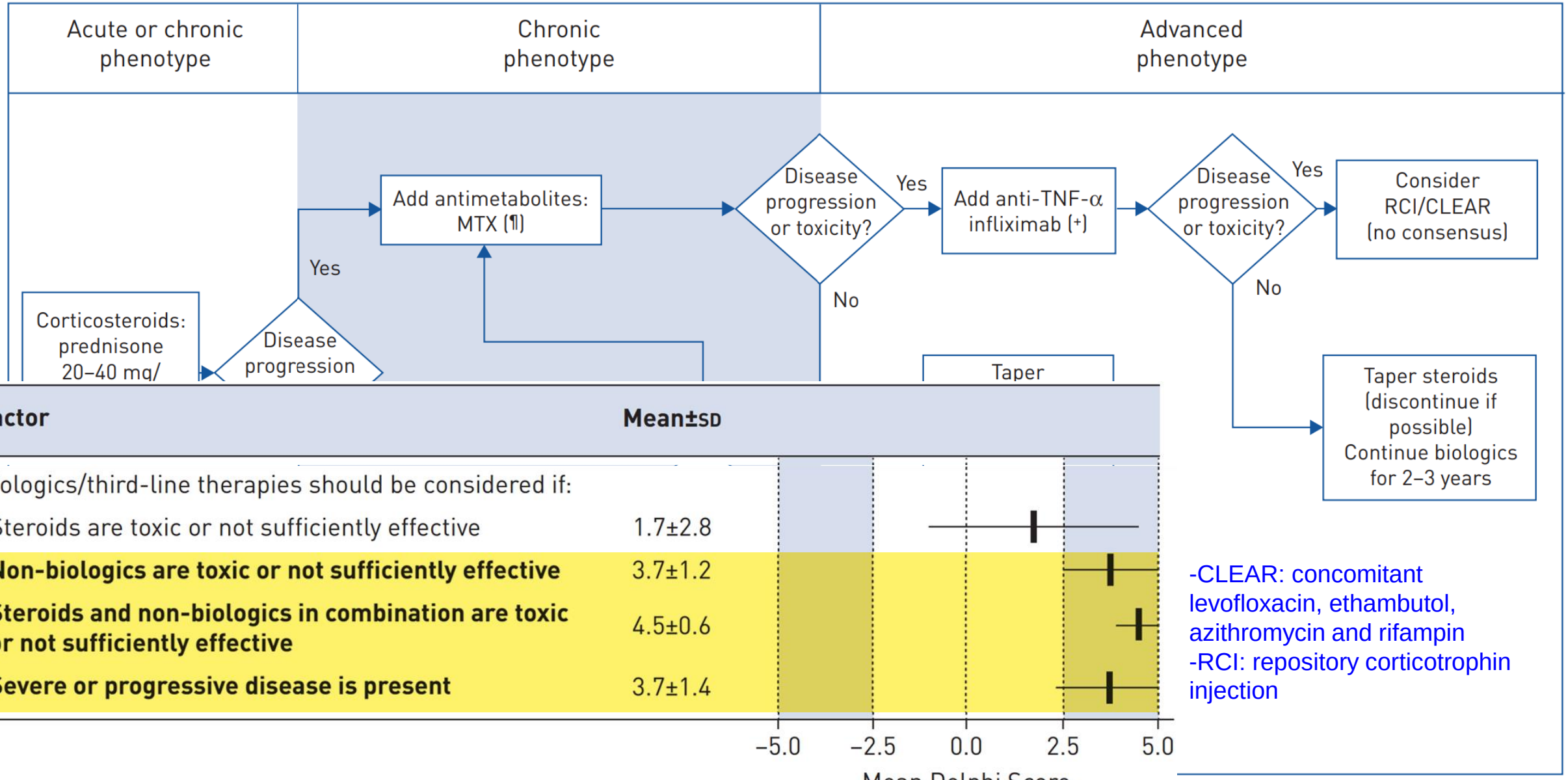


- Retrospective cohort study, 1yr
- Similar in
  - Improving lung function
  - Prednisone dose reduction
  - Benefit on extrapulmonary disease
- Infection: AZA>MTX

  (34.6% vs. 18.1%, p=0.01)

CHEST 2013; 144(3):805–812

Treatment algorithm for symptomatic or organ-threatening sarcoidosis



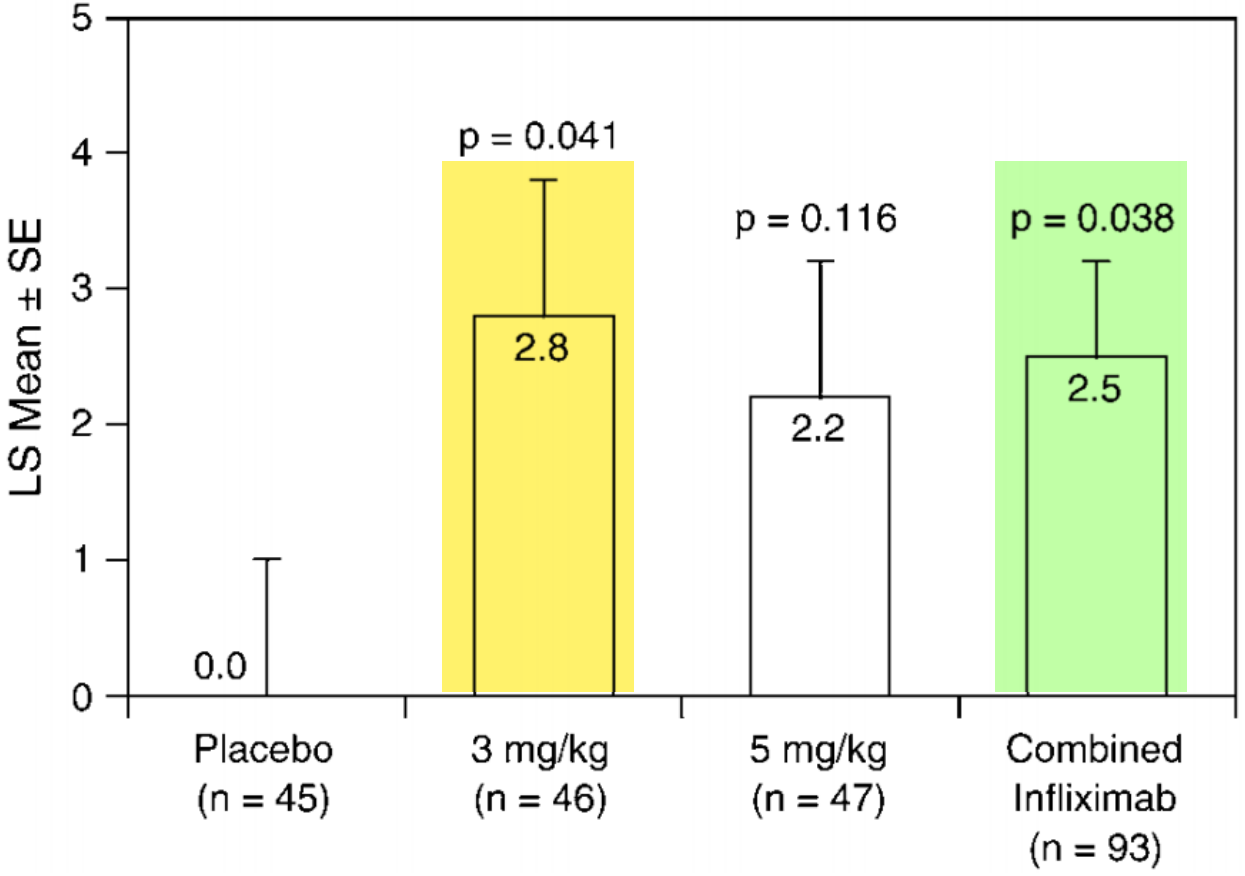
Factor	Mean±SD
Biologics/third-line therapies should be considered if:	
Steroids are toxic or not sufficiently effective	1.7±2.8
Non-biologics are toxic or not sufficiently effective	3.7±1.2
Steroids and non-biologics in combination are toxic or not sufficiently effective	4.5±0.6
Severe or progressive disease is present	3.7±1.4

-CLEAR: concomitant levofloxacin, ethambutol, azithromycin and rifampin
-RCI: repository corticotrophin injection

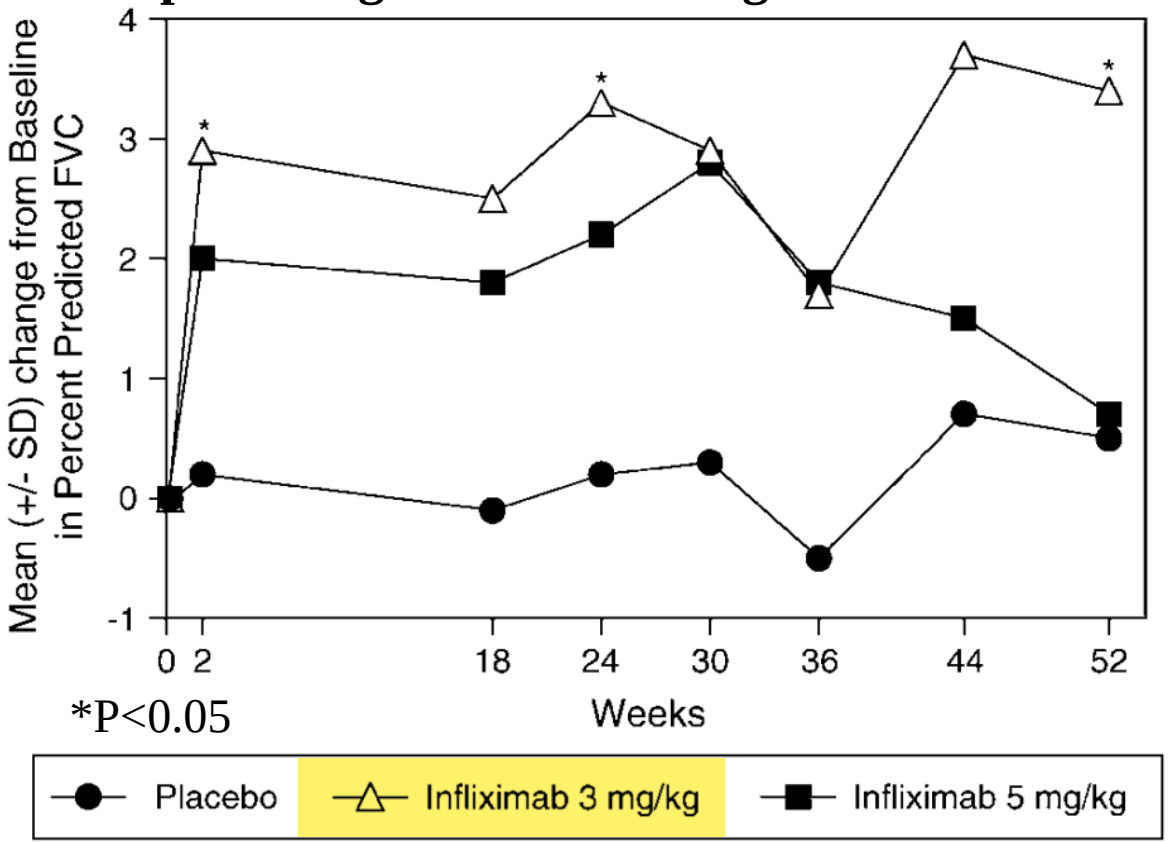
Eur Respir Rev 2020; 29: 190146

Phase 2, DB-RCT, infliximab vs. placebo, 50%<FVC<85%

Change from baseline to Week 24 in FVC (%)



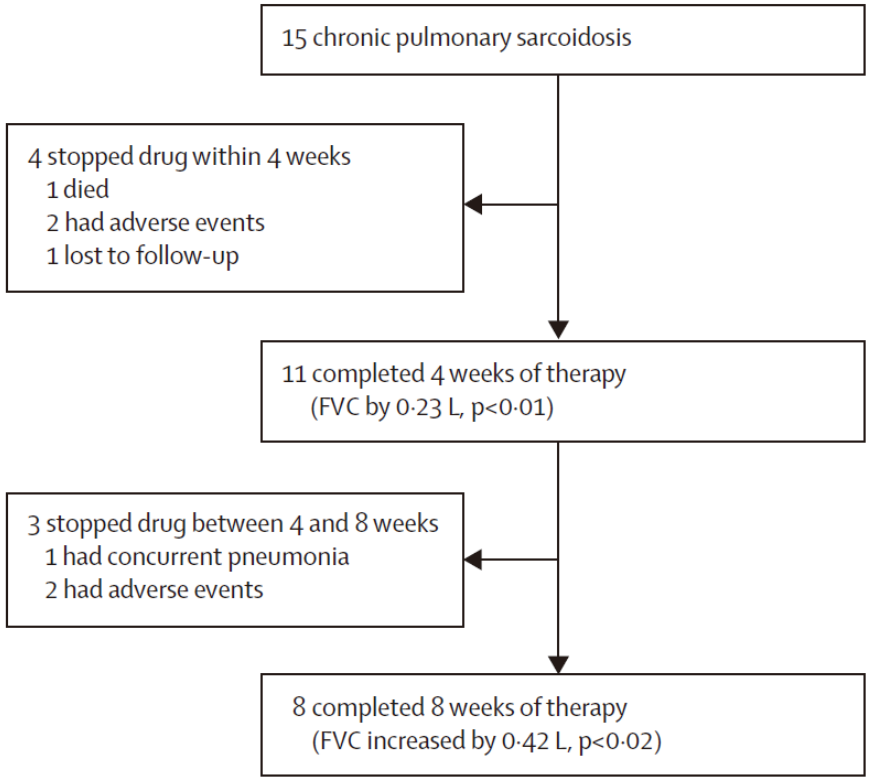
Mean (SD) changes from baseline in percentage of FVC through Week 52



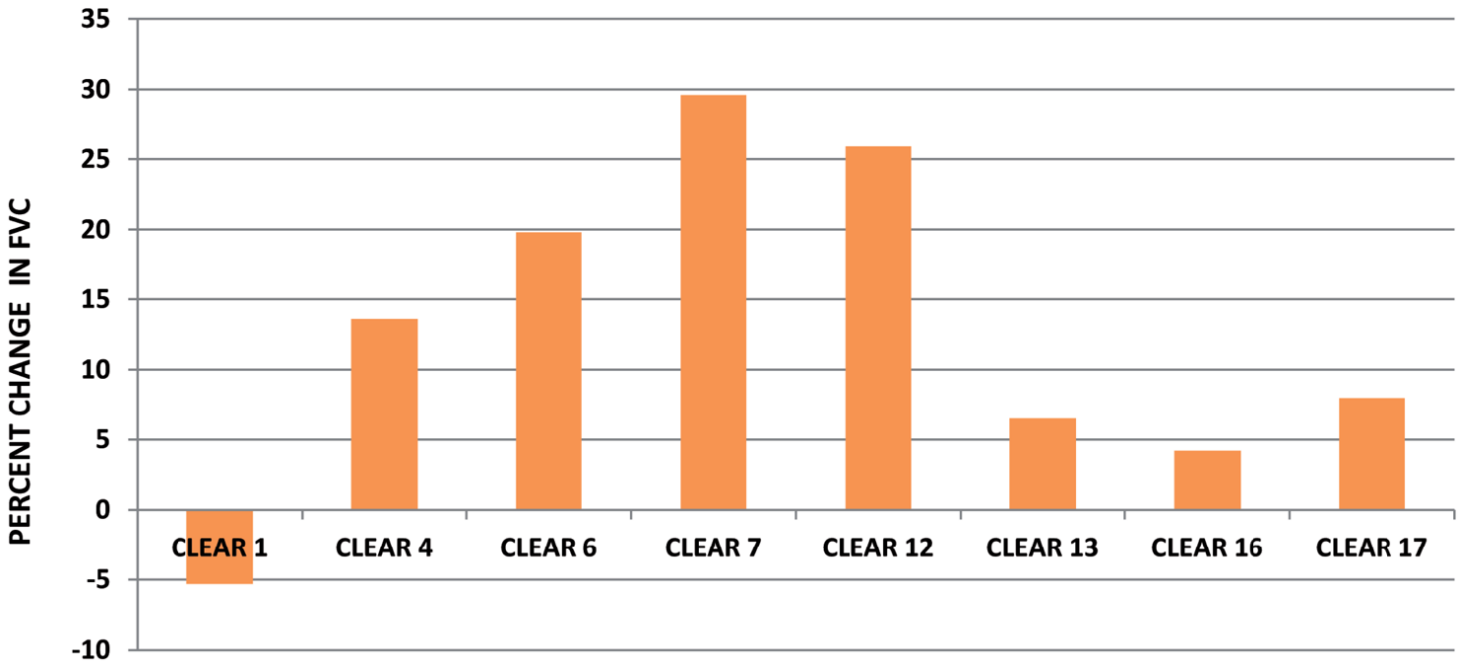
Am J Respir Crit Care Med. 2006 Oct 1;174(7):795-802.

Effects of broad-spectrum antimycobacterial therapy on chronic pulmonary sarcoidosis

Levofloxacin + Ethambutol + Azithromycin + Rifampin



Open label, phase Ib, single-center study (8wks)



The CLEAR regimen is associated with improved absolute FVC, as well as increased functional capacity and quality-of-life in selected chronic pulmonary sarcoidosis patients.

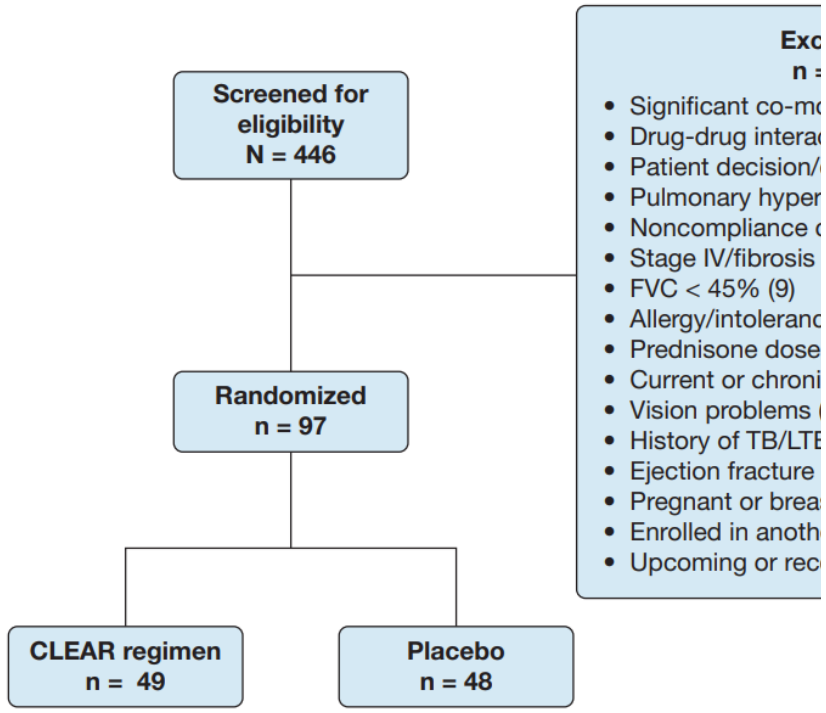
Sarcoidosis Vasc Diffuse Lung Dis. 2013 Nov 25;30(3):201-11.

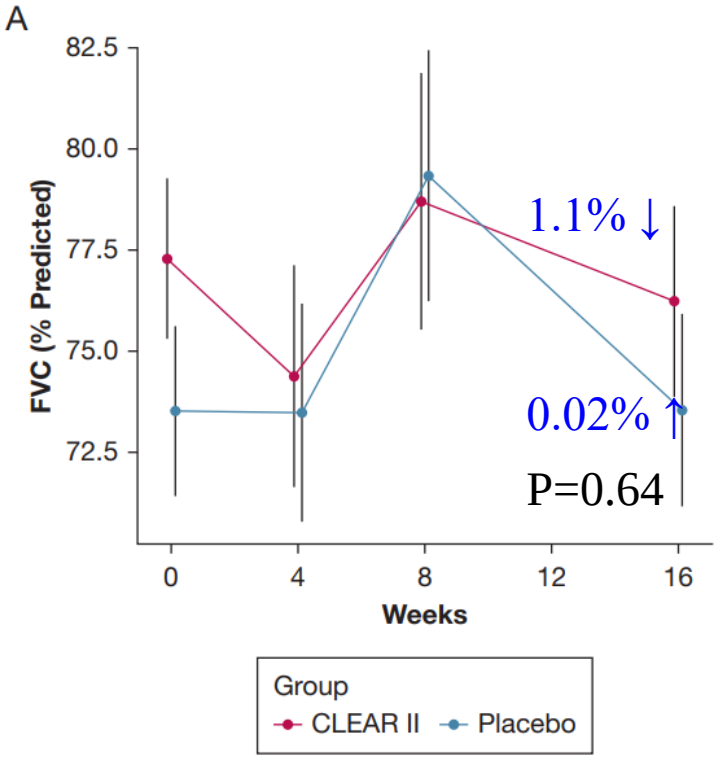
Effects of broad-spectrum antimycobacterial therapy on chronic pulmonary sarcoidosis

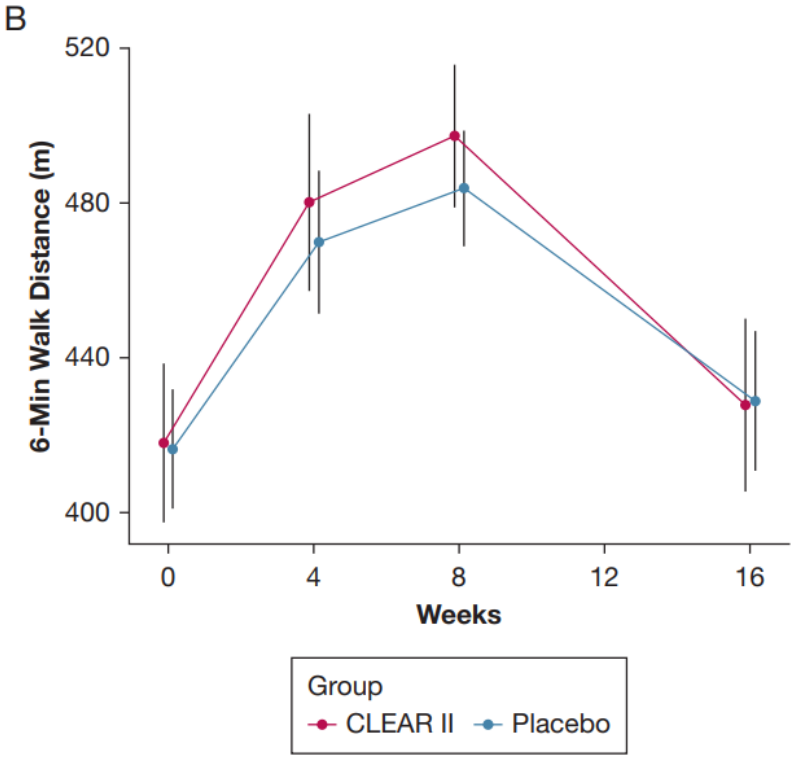
Levofloxacin + Ethambutol + Azithromycin + Rifabutin

Multicenter, DB-RCT, phase II, CLEAR vs. placebo (16wks)
4 durgs (8wks) → 2 drugs (8wks)

FVC or DLco ↓ >5%/24 months
Radiologic progression







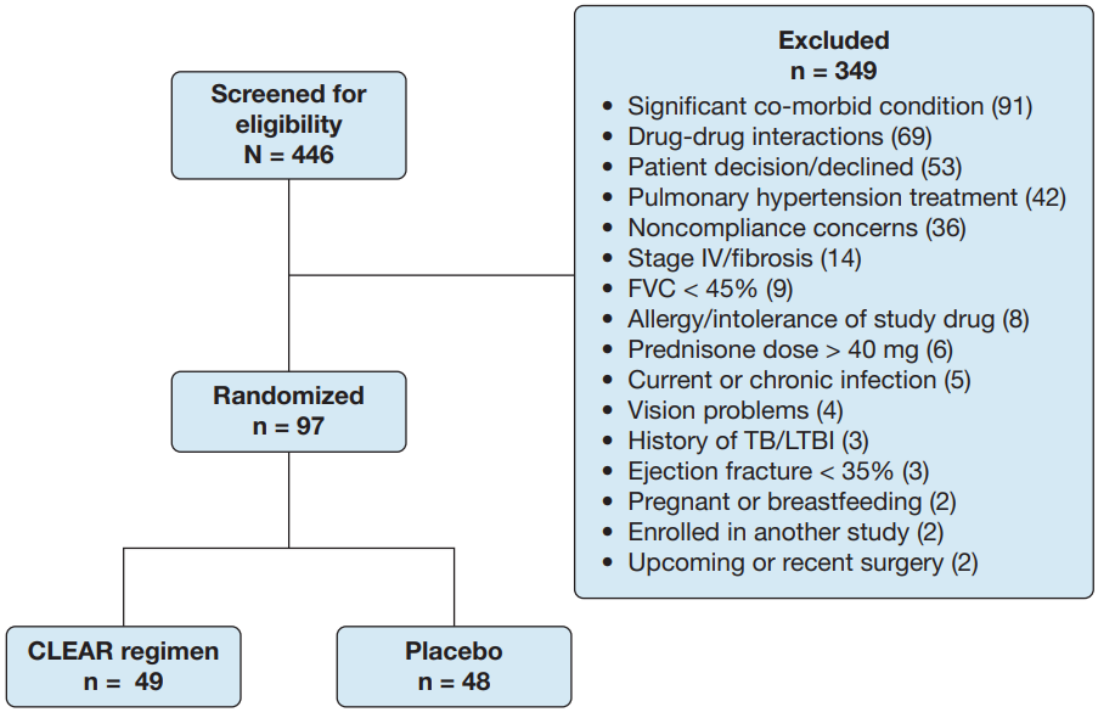
CHEST 2021; 159(5):1902-1912

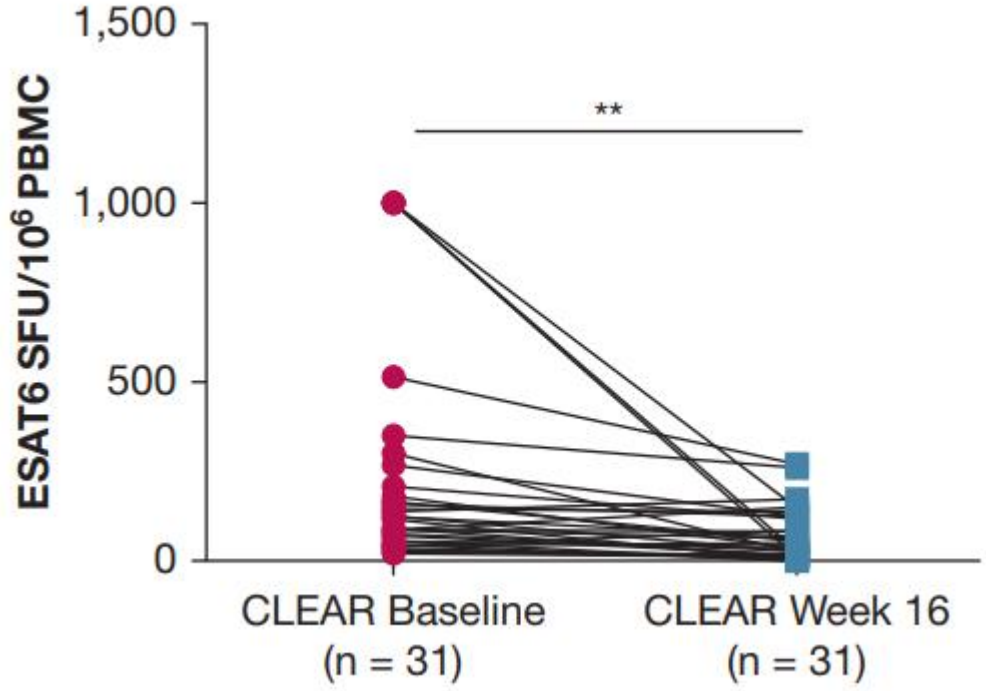
Effects of broad-spectrum antimycobacterial therapy on chronic pulmonary sarcoidosis

Levofloxacin + Ethambutol + Azithromycin + Rifabutin

Multicenter, DB-RCT, phase II, CLEAR vs. placebo (16wks)
4 durgs (8wks) → 2 drugs (8wks)

FVC or DLco ↓ >5%/24 months
Radiologic progression





CHEST 2021; 159(5):1902-1912

The NEW ENGLAND JOURNAL of MEDICINE

DBRCT, phase 3 trial, 15 countries, nintedanib 150mg bid vs. placebo

ORIGINAL ARTICLE

INBUILD trial

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

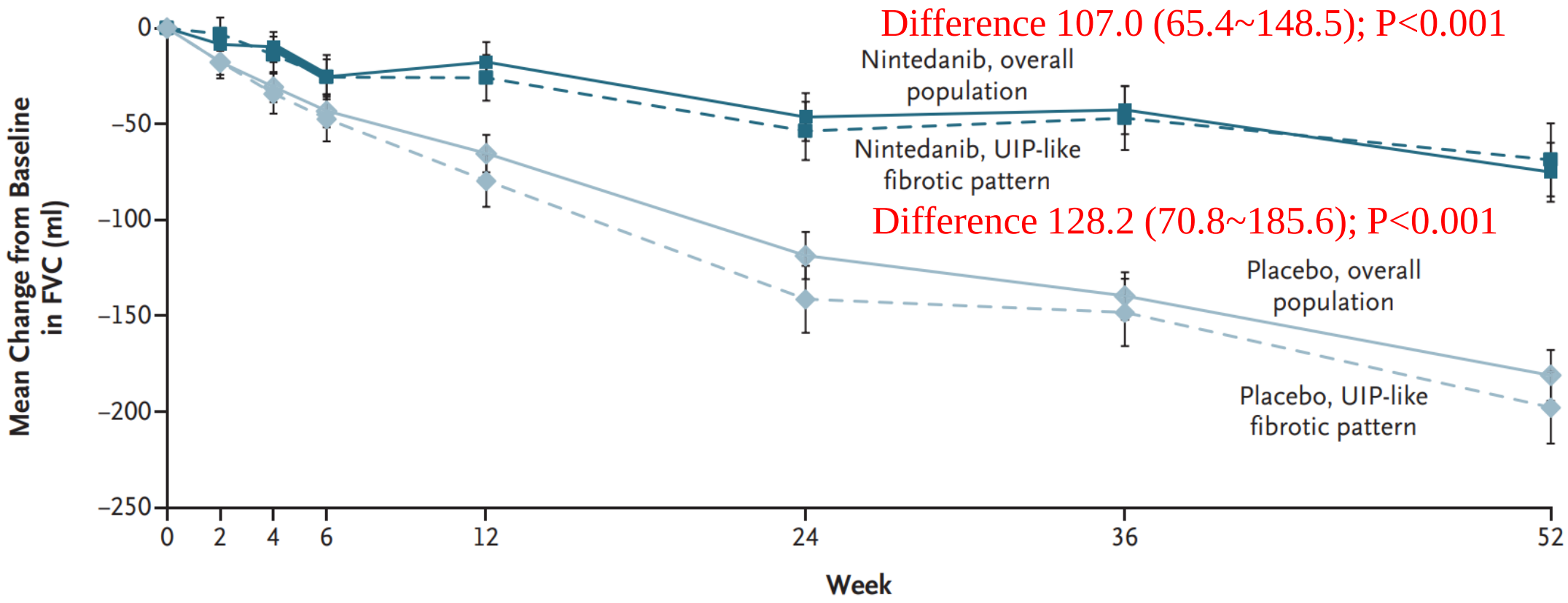
K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

52 weeks

FVC >10% ↓
FVC 5~10% ↓ + respiratory symptoms ↑ or fibrosis on HRCT ↑
Respiratory symptoms ↑ + fibrosis on HRCT ↑

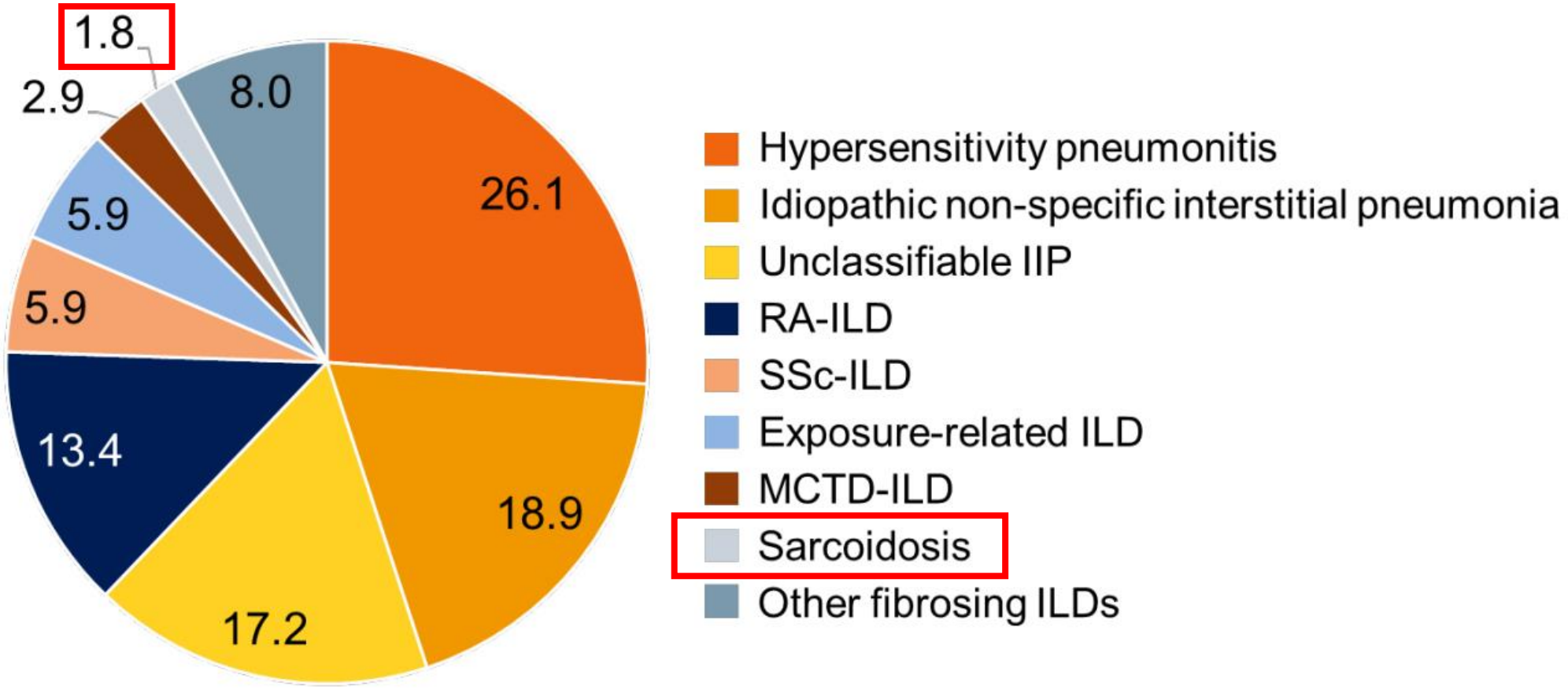
N Engl J Med 2019; 381:1718-1727

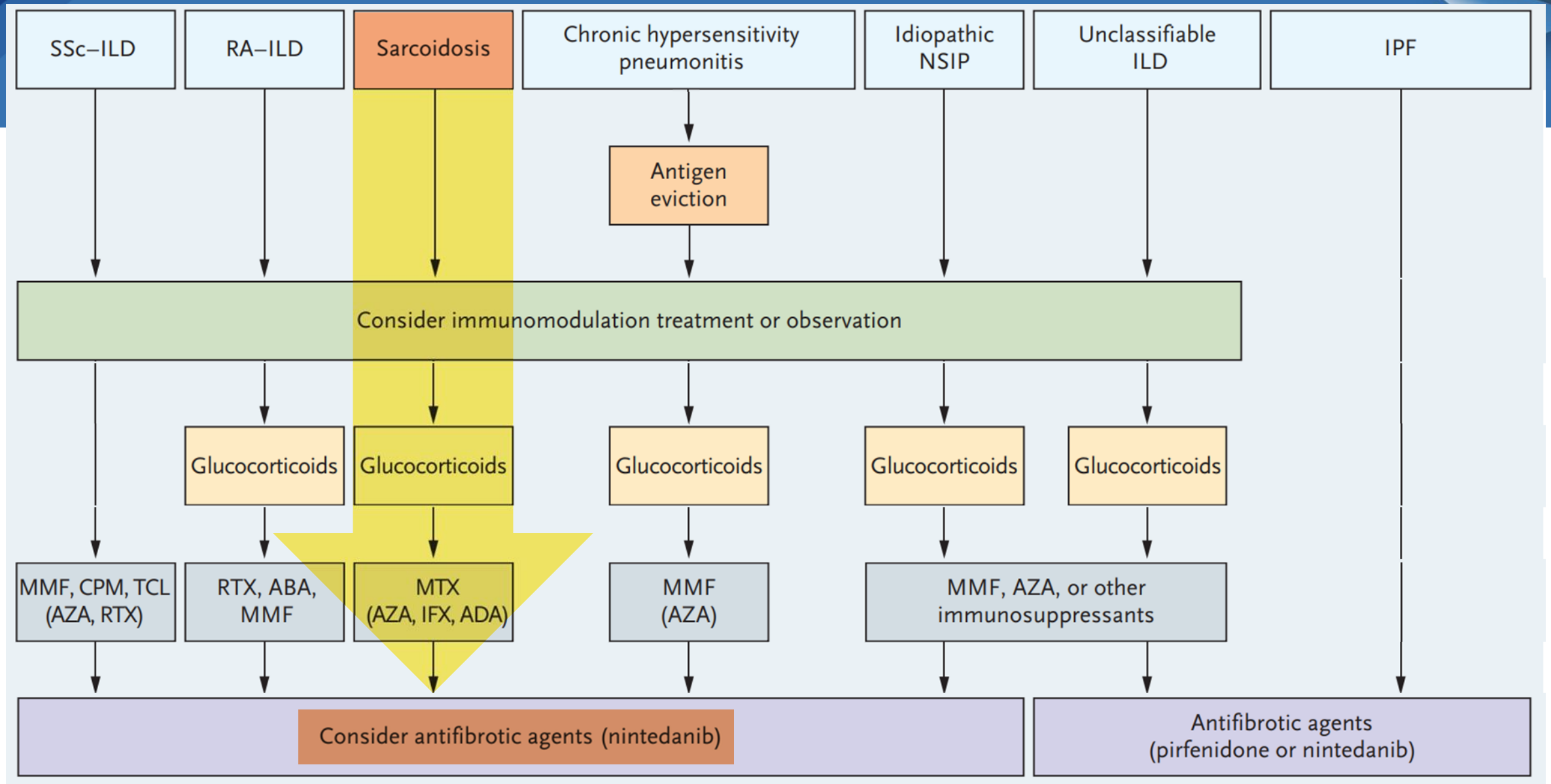
FVC 감소



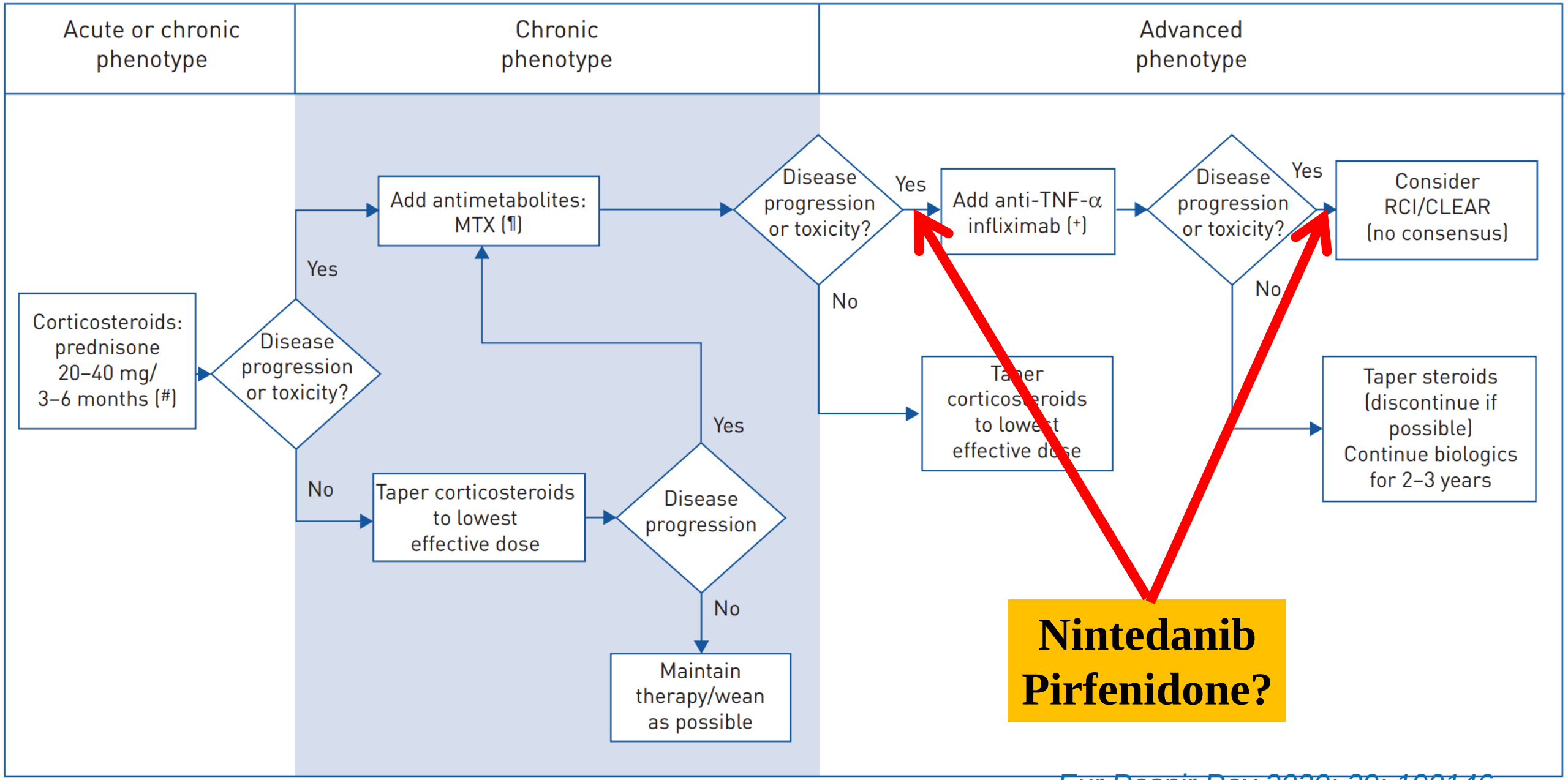
N Engl J Med 2019; 381:1718-1727

9 disease groups





N Engl J Med 2020; 383:958-968



Eur Respir Rev 2020; 29: 190146

Guidance for follow-up

Table 4 Guidance for follow-up. Adapted from Valeyre[151]

	Frequency	Duration	Discharge
Lofgren's syndrome or stage I chest X-ray	6 monthly	2 years	Yes
Stage II to IV chest X-ray	3 to 6 monthly or Annually (depending on clinical suspicion of a change in disease behaviour)	2 years or Long-term	No
Significant extrapulmonary disease	3 to 6 monthly	Long-term	No
Withdrawal from steroid therapy	2 to 3 monthly or 3 to 6 monthly	1 year or Minimum 3 years after cessation	No

Thillai M, et al. Thorax 2020;0:1–17.

Summary

- Diagnosis of sarcoidosis is based on clinical presentation, non-necrotizing granuloma and exclusion of alternative causes.
- EBUS-TBNA is preferred tissue biopsy in patients with mediastinal and/or hilar lymphadenopathy.
- Initial screening tests for asymptomatic extrapulmonary sarcoidosis are eye exam, CBC, Ca, Cr, ALP, and EKG.
- Symptomatic patients with impaired PFT or infiltrates are recommended be treated.
- Glucocorticoids is initial therapy, and MTX as a second-line durg is considered in severe or extrapulmonary disease requiring prolonged treatment.