Understanding the Complexities of Sarcoidosis

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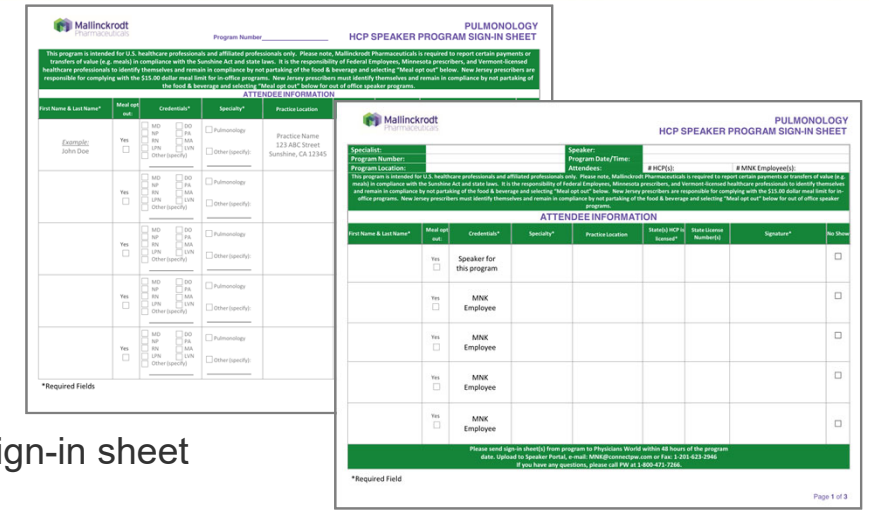


In This Presentation

- Sarcoidosis Etiology
- Clinical Presentation and Diagnosis
- Advanced Pulmonary Sarcoidosis
- Treating Symptomatic Sarcoidosis

Sarcoidosis Etiology

Introduction to Sarcoidosis[1,2]

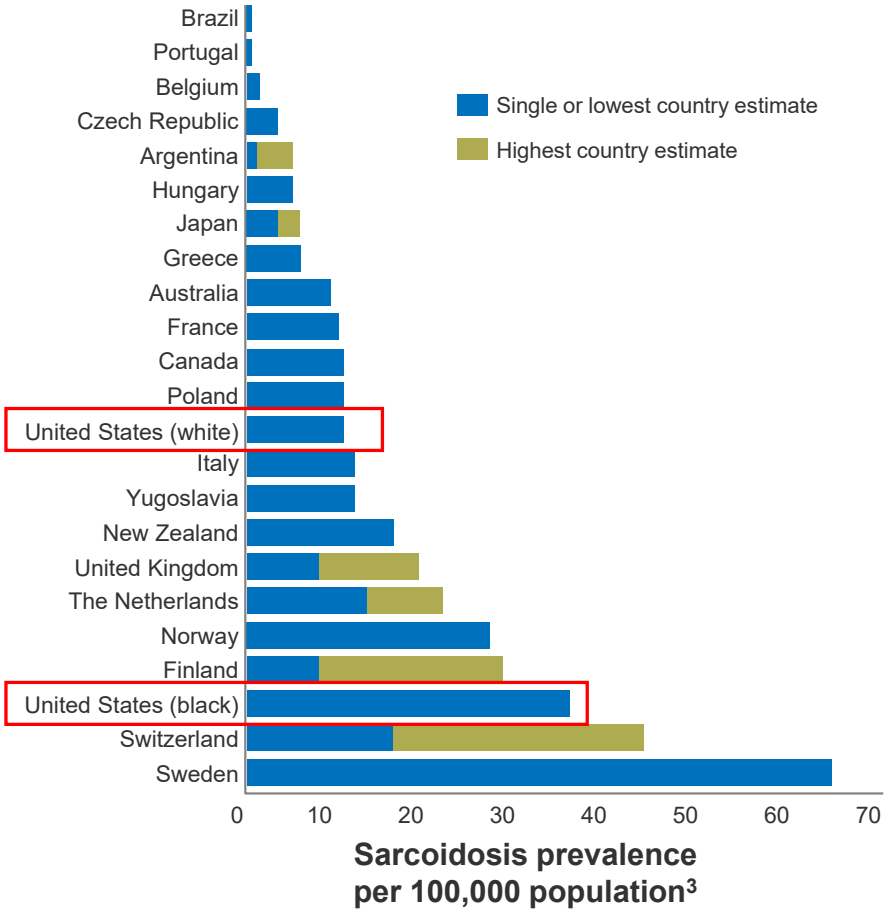
Description	Systemic granulomatous disease of unknown etiology
Pathology	Noncaseating epithelioid granulomas in affected organ(s)
Affected organs	Can involve any organ, including the lungs, skin, eyes, heart and neurologic system

1. Jara-Palomares L et al. Clinical manifestations of sarcoidosis. In: *Sarcoidosis*. 2013:109-143. **2.** Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165..

Sarcoidosis Affects Approximately 185,000 Individuals in the United States[1]

United States: ~185,000[1]

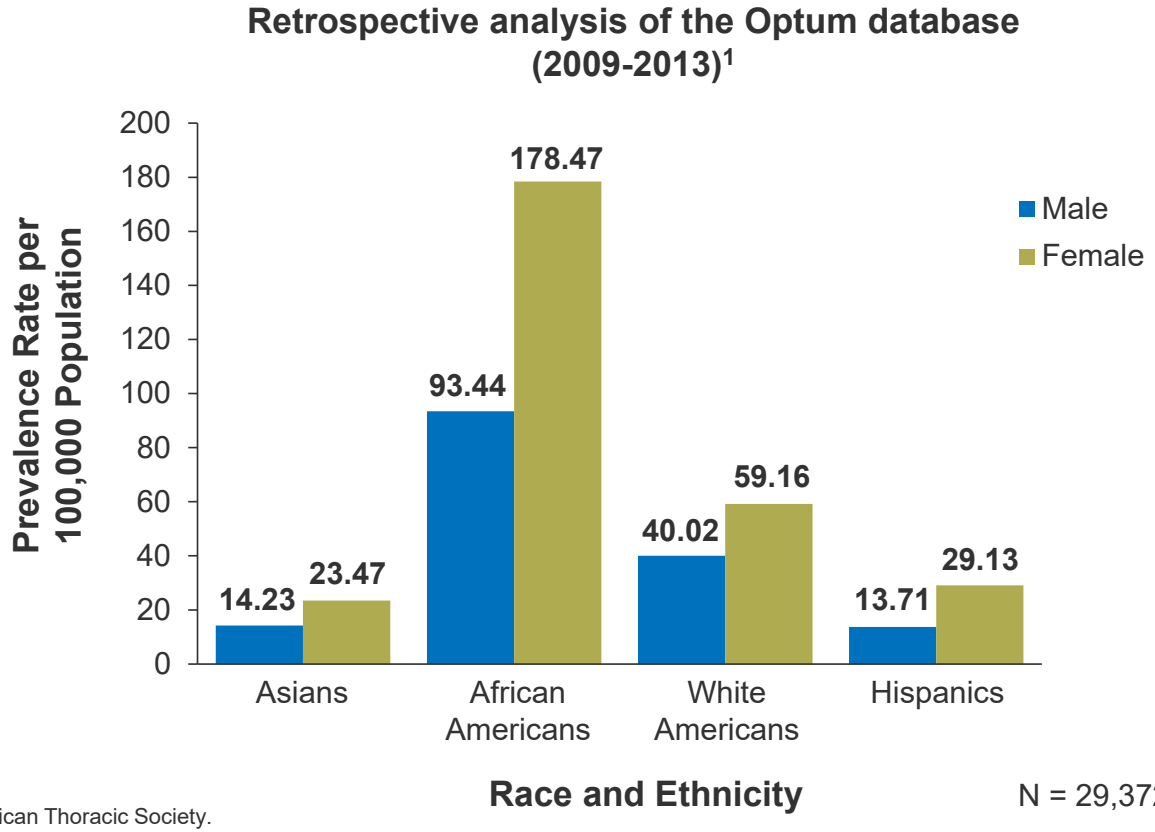
- A study examining prevalence in central Ohio found that regional prevalence may be as much as 4-fold greater than previously estimated, suggesting the true prevalence of sarcoidosis is underestimated.[2]



1. Baughman RP et al. Ann Am Thorac Soc. 2016;13:1244-1252. **2**. Erdal BS et al. *Respir Med*. 2012;106:893-899. **3.** Denning DW et al. *Eur Respir J*. 2013;41:621-626.

Sarcoidosis Has an Increased Incidence in Older Population and Is Most Common in African Americans[1]

- Although earlier studies characterized sarcoidosis as a disease of young people, recent studies have shown an increased incidence in the older population.[1]
  - Among patients with sarcoidosis, 59% were 55 years of age or older.[1]
- Sarcoidosis was 3× more prevalent in African American women than in white American women.[1]
  - In a separate study, the disease was more severe in African Americans than in white Americans.[2]



N = 29,372.

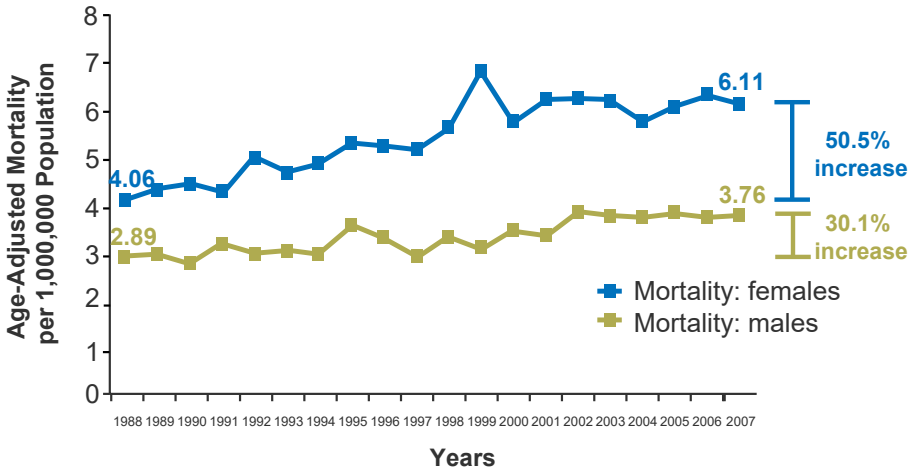
1. Baughman RP et al. *Ann Am Thorac Soc*. 2016;13:1244-1252. *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society. **2**. Judson MA et al. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29:119-127.

Sarcoidosis Is Associated With High Disease Burden[1-5]

Increased Mortality

- Average age- and sex-adjusted sarcoidosis-related mortality was 4.32 per 1,000,000 population in the United States over a 20-year period.[1]
- The age-adjusted mortality rate for non-Hispanic black Americans is 12 times higher than for whites.[5]

Retrospective analysis of data collected from the National Center for Health Statistics (1988-2007; N = 46,450,489)



Decreased Quality of Life (QOL)

- Patients with sarcoidosis had significant decrements in their QOL.[2-4]

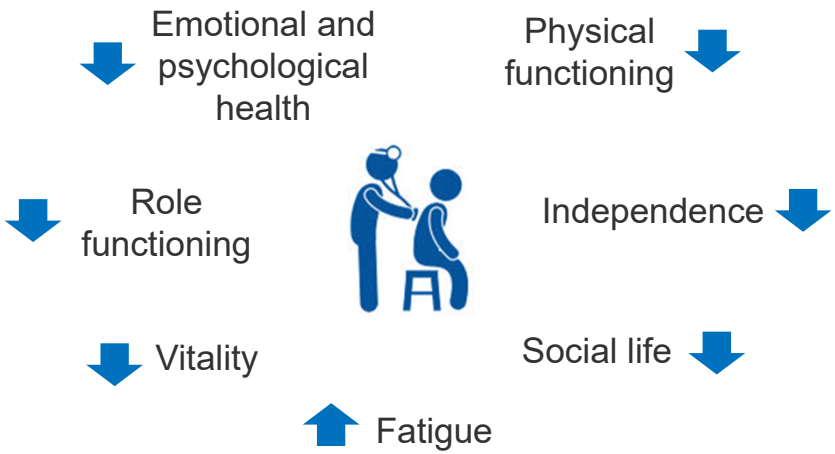
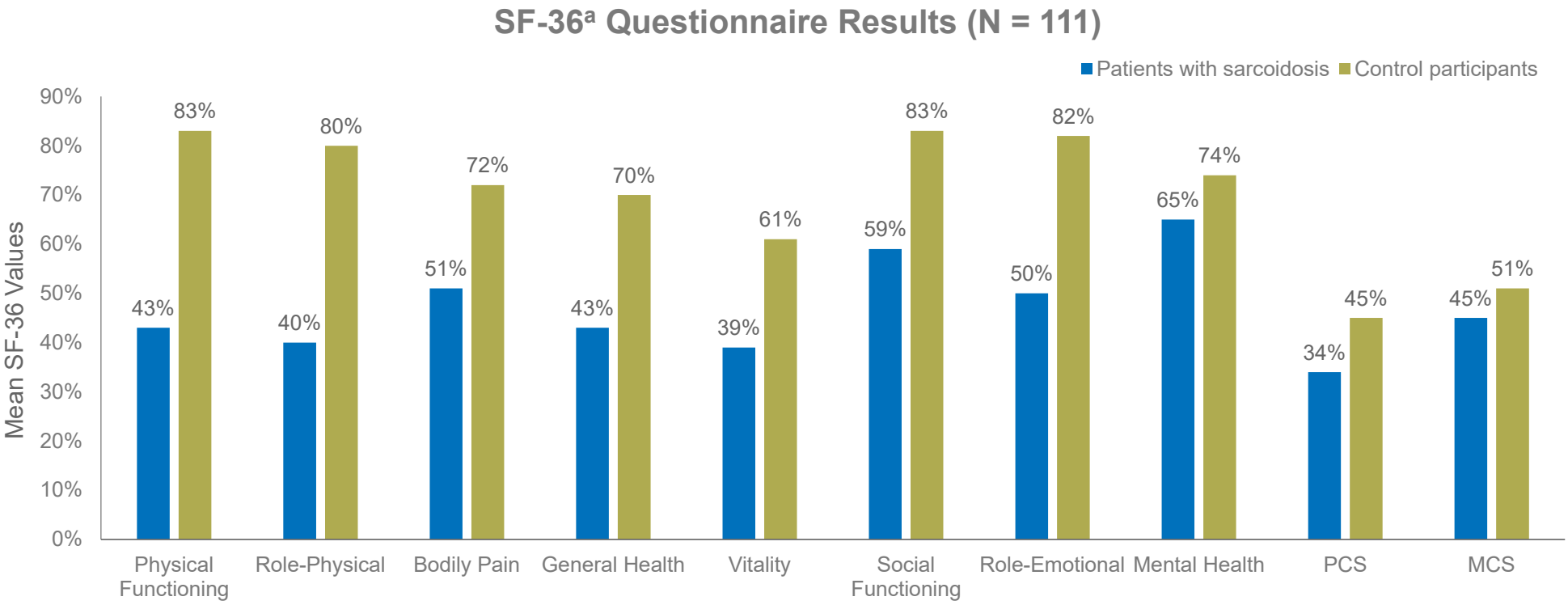


Figure reproduced and adapted with permission from Swigris JJ et al.

1. Swigris JJ et al. *Am J Respir Crit Care Med*. 2011;183:1524-1530. **2.** Cox CE et al. *Chest*. 2004;125(3):997-1004. **3.** De Vries J et al. *Semin Respir Crit Care Med*. 2010;31(4):485-493. **4.** de Boer S et al. *Respirology*. 2014;19(7):1019-1024. **5.** Mirsaeidi M et al. *Chest*. 2015;147:438-449.

Patients With Sarcoidosis Have Decrements in Physical and Mental Function

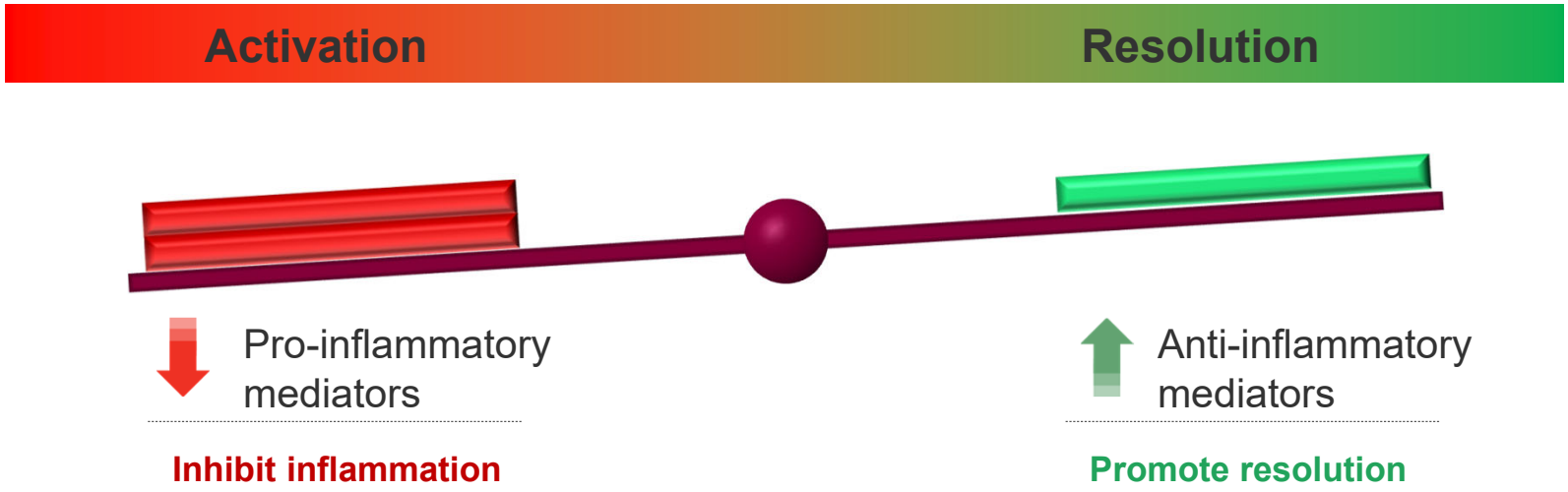


MCS = mental component score; PCS = physical component score.
[a]SF-36 is a health measurement tool that assesses impact of disease and treatment on functional status and well-being of patient (lower scores reflect worse outcomes).
Cox CE et al. *Chest*. 2004;125(3):997-1004.

Immune Dysregulation Is Believed to Lead to Chronic Disease[1,2]

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165. **2.** Broos CE et al. *Front Immunol*. 2013;4:437.

Mitigating Immune Diseases Primarily Focuses on Restoring Immune Balance[1,2]

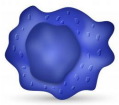


- Processes of activation and resolution are key in balancing the immune response.[1,2]
- The melanocortin system may play an important role in anti-inflammatory and proresolution processes.[3,4]

1. Tabas I and Glass CK. *Science*. 2013;339:166-172. **2.** Silverman M et al. *Viral Immunol*. 2005;18:41-78. **3.** Ahmed TJ et al. *Int J Inflam*. 2013;2013:985815. **4.** Catania A et al. *Pharmacol Rev*. 2004;56:1-29.

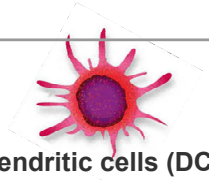
Sarcoidosis Is a Disease of Immune Dysregulation Involving Multiple Immune Cells[1-3]

Unknown antigen[1-3] → Immune response → Immune dysfunction



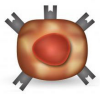
Macrophages

- Migrate to affected tissue as one of first responders[1]
- Release TNF-α inducing vasodilation and monocyte/lymphocyte infiltration[1]
- Release pro-inflammatory cytokines (eg, IL-1, -6, -12, -23) promoting[1]:
  - Leukocyte infiltration
  - T-cell activation
  - T_{reg} inhibition
  - T-cell apoptosis inhibition
- Lead to[1]:
  - Cell-mediated granulomatous inflammation
  - Tissue damage/fibrosis



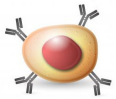
Dendritic cells (DCs)

- Inflammation causes DC activation, maturation and migration to lymph nodes[2]
- Drive T-cell expansion and Th1 polarization[2]
- Produce a battery of mediators that facilitate the sarcoid immune reaction[3]
- TNF-α production leads to CD4+ T-cell proliferation[3]



T cells

- CD4+ T cell infiltrates at site of inflammation[1]
- T-cell lymphopenia in peripheral blood[1]
- Abnormal T-cell response in nongranulomatous tissue[1]
- Initial Th1 response during inflammation shifts to Th2 leading to fibrosis[1]
- CD8+ T cells accumulate in the sarcoid lung[2]
- Th17 T cells are increased in inflammatory tissue and peripheral blood[1]
- T_{regs} are increased outside granulomas but exhibit decreased function[1]



B cells

- Surround granulomas in affected tissues[1]
- Reduced number of memory B cells and plasma cells in blood[1]
- B-cell NFκ-B levels are reduced and may affect B-cell responses and proliferation[1]

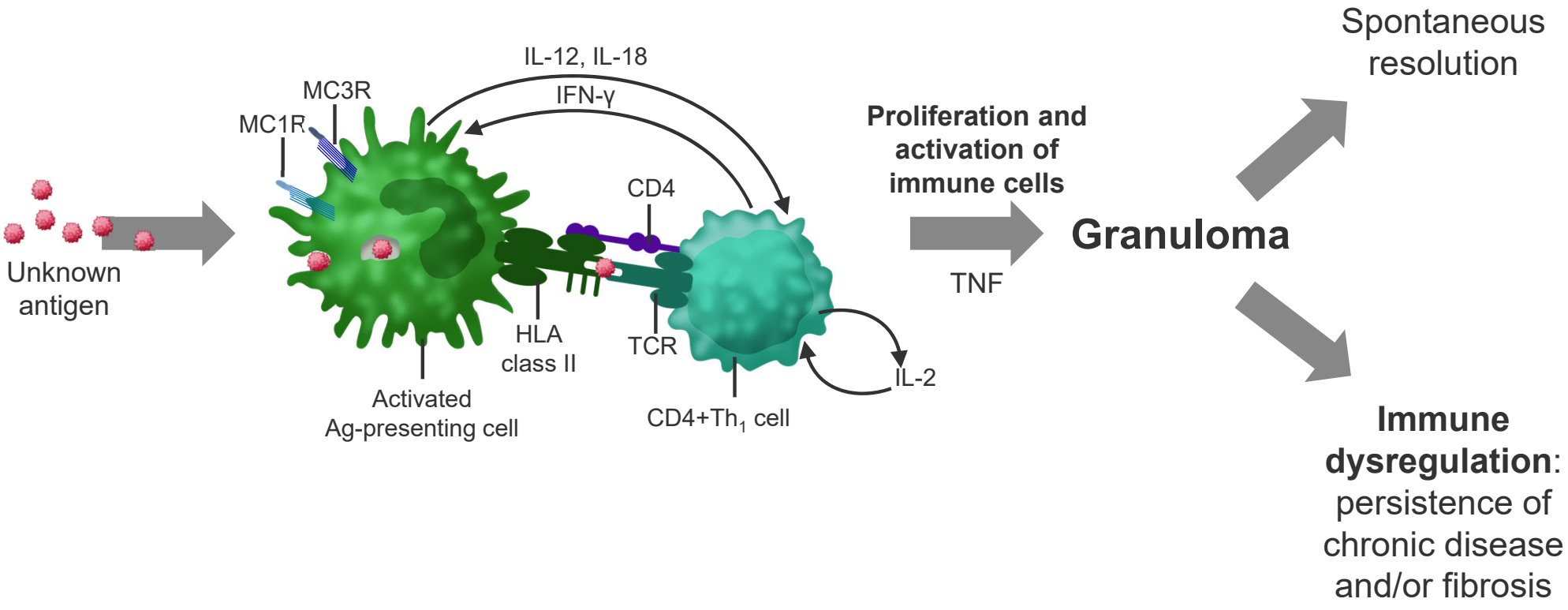
Natural killer T cells

- Reduced numbers in blood and bronchoalveolar lavage may account for persistence of sarcoidosis[3]
- Moderate CD4-mediated immune response[3]

IL = interleukin; TNF-α = tumor necrosis factor α; T_{reg} = regulatory T cells.

1. Timmermans WM et al. *Clin Transl Immunology.* 2016;5(12):e118. **2.** Mortaz E et al. *Iran J. Allergy Asthma Immunol.* 2014;13(5):300-306. **3.** Loke WS et al. *Int J Chronic Dis.* 2013;2013:928601.

Immune Dysregulation, Granuloma Formation May Result in Persistent Chronic Disease and Fibrosis[1,2]

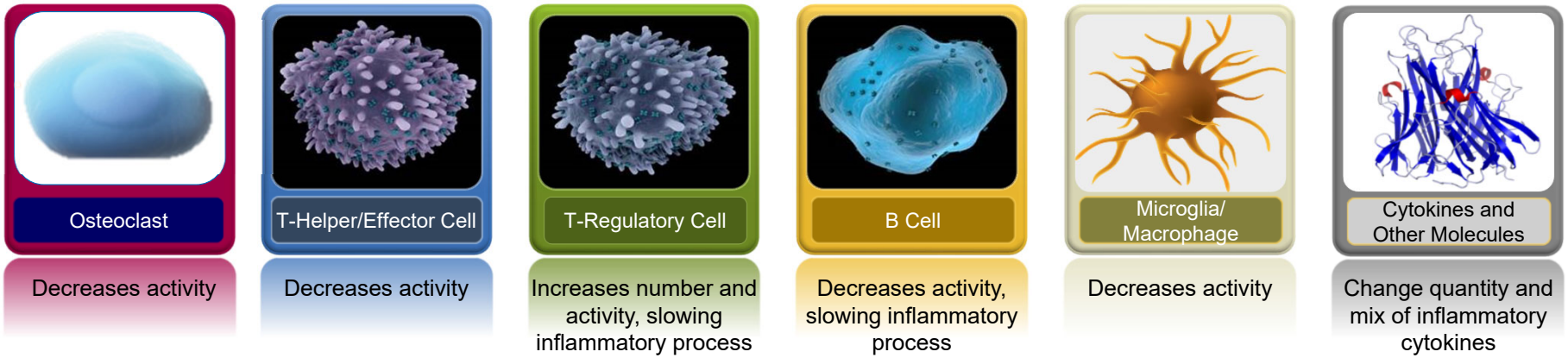


Ag = antigen; HLA = human leukocyte antigen; IFN = interferon; MC1R = melanocortin receptor 1; MC3R = melanocortin receptor 3; TCR = T-cell receptor; TNF = tumor necrosis factor.

1. Adapted with permission from Baughman RP et al. *Am J Respir Crit Care Med*. 2011;183:573-5811. **2.** Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165.

The Melanocortin System Is Believed to Be Involved in a Variety of Immunological and Physiological Processes[1-3]

- The melanocortin system may play an integral role in a diverse array of biological effects, including[1-3]:
  - Regulation of immune cell adhesion and trafficking
  - Inhibition of NF-κB signaling and activation
  - Steroidogenesis



- The natural melanocortins α-, β-, and γ-MSH and ACTH bind to melanocortin receptors expressed on cell surfaces.[1]

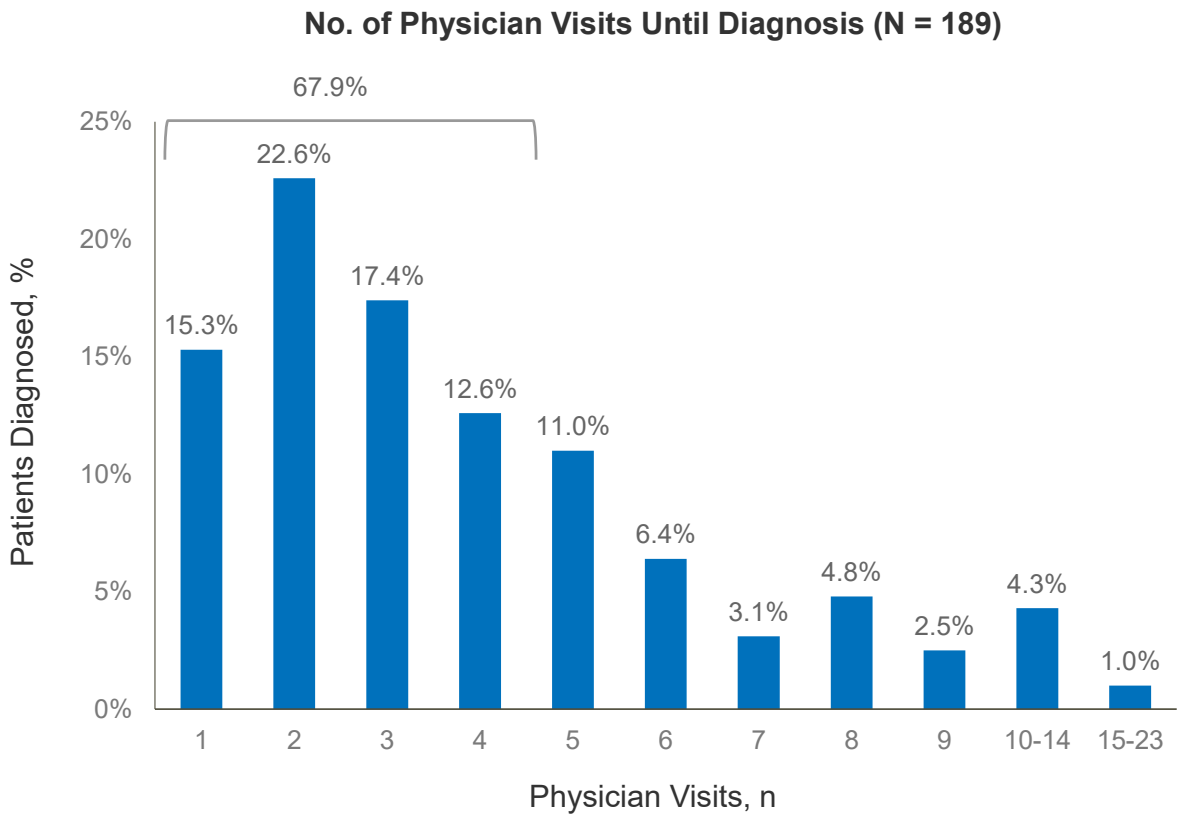
ACTH = adrenocorticotropic hormone; MSH = melanocyte-stimulating hormone; NF-κB = nuclear factor kappa light-chain enhancer of activated B cells.

1. Brzoska T et al. *Endocr Rev*. 2008;29:581-602. **2.** Catania A et al. *Pharmacol Rev*. 2004;56:1-29. **3.** Gong R. *Nat Rev Nephrol*. 2011;8:122-128.

Clinical Presentation and Diagnosis

Most Symptomatic Patients Required ≥4 Physician Visits Until Diagnosis

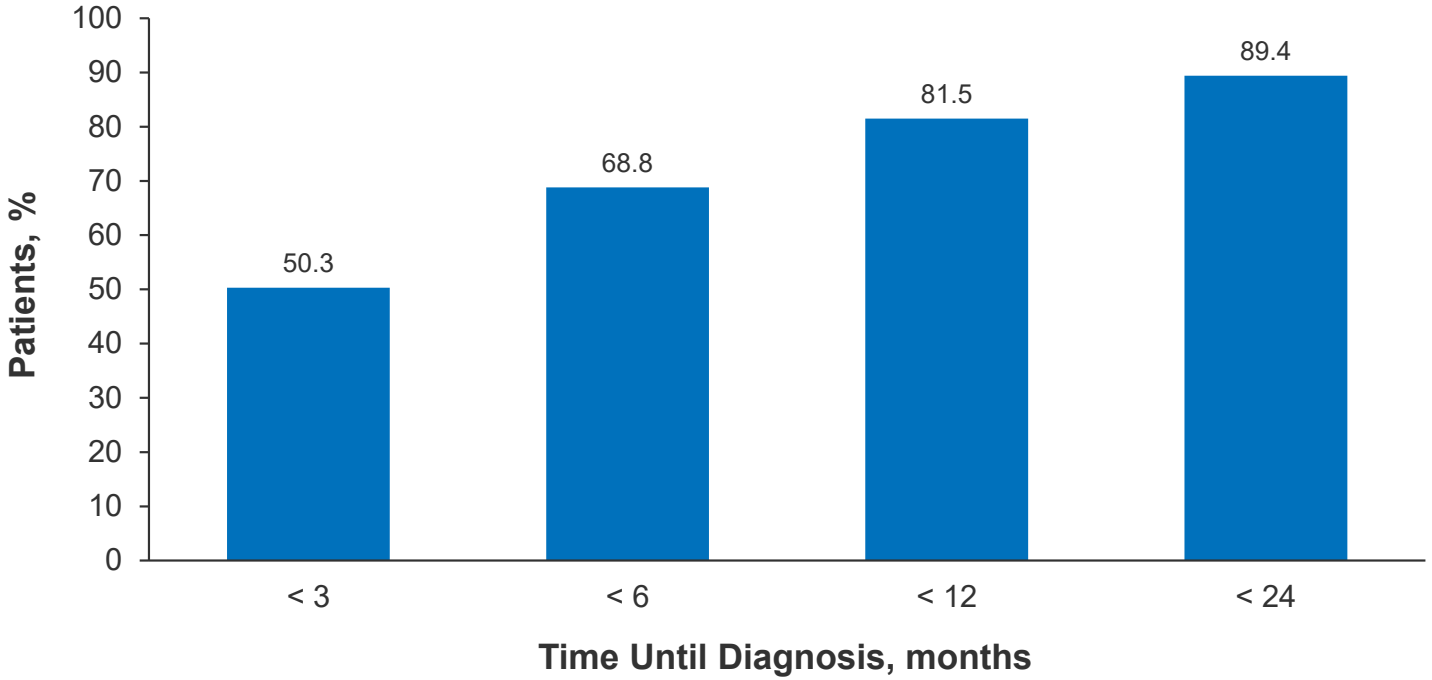
- Only 15.3% of patients were diagnosed on the first physician visit.
- ~46% of patients required ≥4 physician visits until diagnosis.
- >20% of cases required 6 or more visits until the diagnosis was established.
- Multiple factors caused diagnosis and treatment delay.
  - Initial disease was often asymptomatic.
  - Symptoms were nonspecific and could suggest other pulmonary disease.
  - Involvement of any organ system could cause referral to a wide range of specialists.
  - Economic factors and/or other barriers prevented access to appropriate medical care.



Judson MA et al. *Chest*. 2003;123:406-412.

In ~50% of Cases, Sarcoidosis Is Diagnosed More Than 3 Months After Symptom Onset[1]

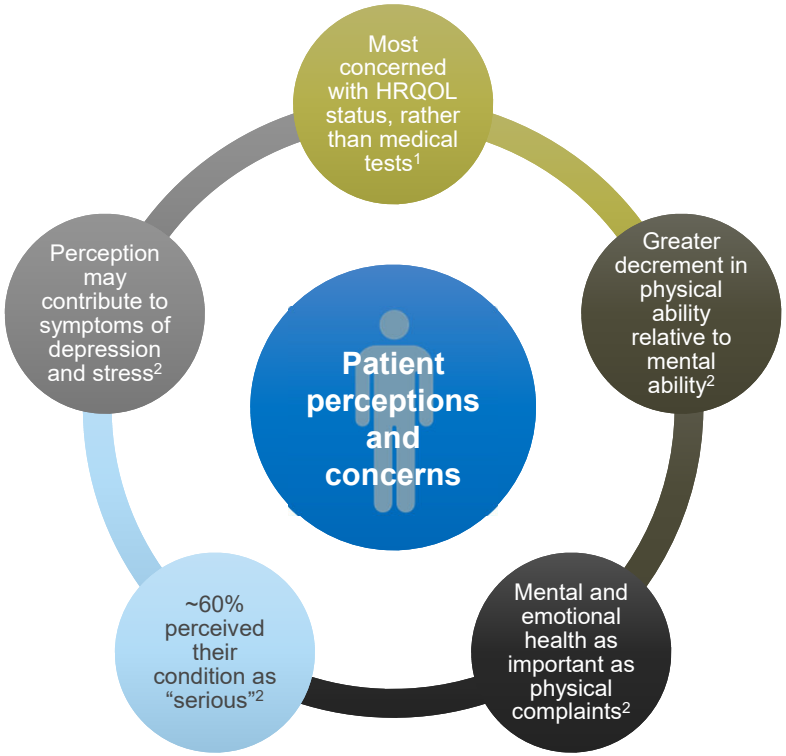
Multicenter observational study following etiology, socioeconomic status and clinical course of patients with sarcoidosis (1996-1999)[1,2]



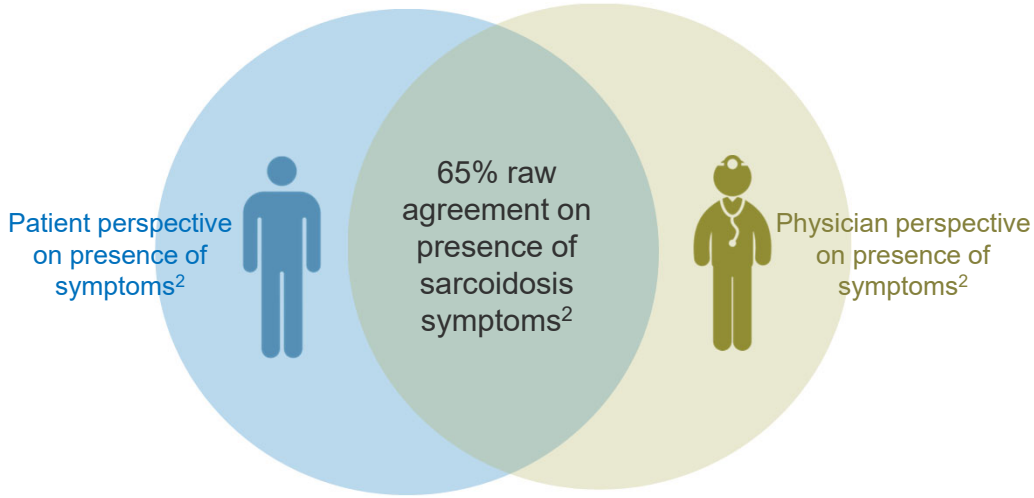
N = 189.

1. Judson MA et al. *Chest*. 2003;123:406-412. **2.** ACCESS Research Group. *J Clin Epidemiol*. 1999;52:1173-1186.

Physician Assessment of Sarcoidosis Correlates Poorly With Patient Self-Assessment[1,2]



- Physicians and patients had only fair agreement about the presence and importance of symptoms attributable to sarcoidosis.[2]



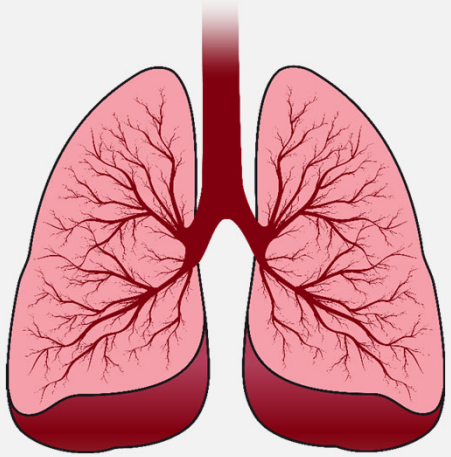
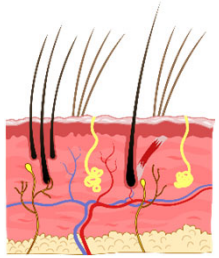
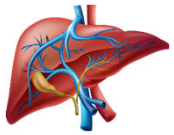
HRQOL = health-related QOL.

1. Judson MA et al. *Am J Respir Crit Care Med*. 2015;191(7):786-795. **2.** Cox CE et al. *Chest*. 2004;125(3):997-1004.

Sarcoidosis Involves Both Pulmonary and Extrapulmonary Manifestations

The Lung Is the Most Common Organ Involved

Large single-cohort retrospective analysis at the Medical University of South Carolina Multidisciplinary Sarcoidosis Clinic (1999-2010)

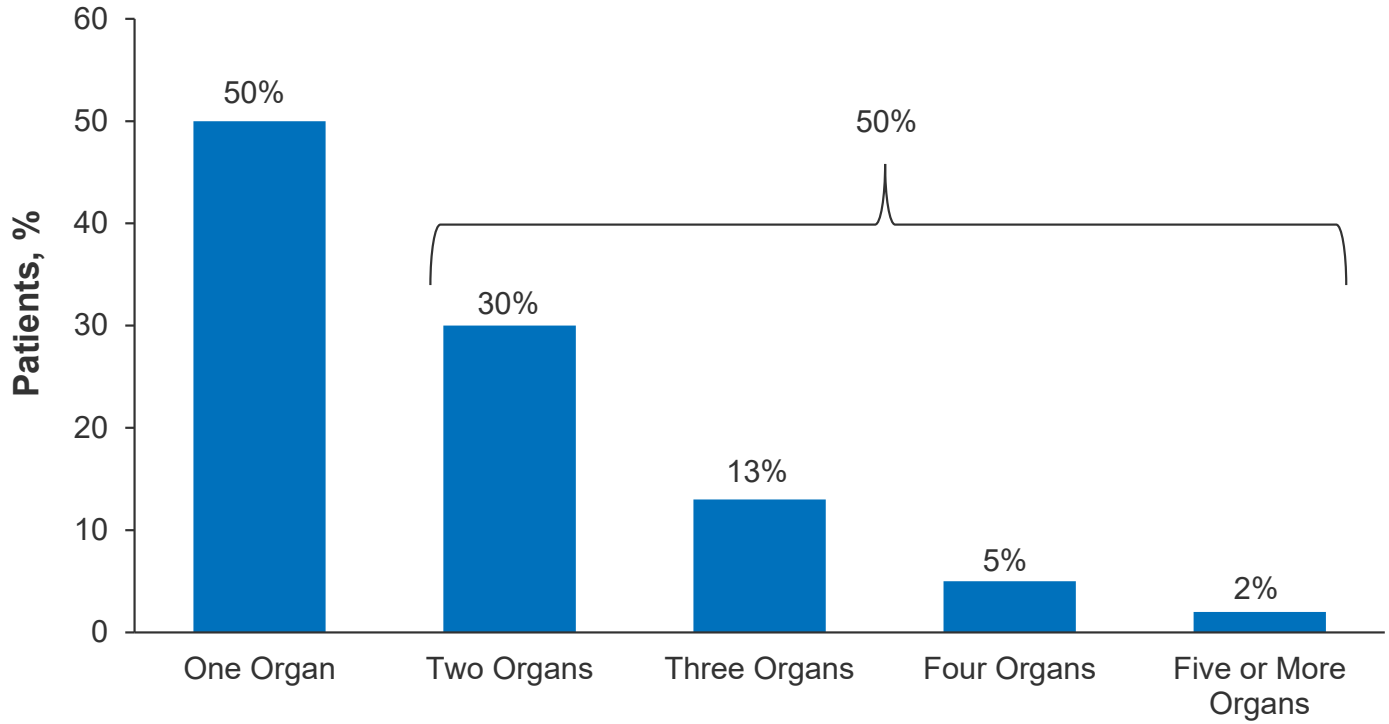
Lungs	Skin	Eyes	Liver	Others
				Lymph nodes Ear, nose, throat Neurologic Bone, marrow Spleen Bone, joints Cardiac Salivary, glands Muscle Renal
89%	**26%**	**23%**	**20%**	**< 15%**

N = 1582.

Judson MA et al. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29:119-127.

Sarcoidosis Affects Multiple Organs in 50% of Cases[1,2]

Multicenter observational study following etiology, socioeconomic status and clinical course of patients with sarcoidosis (1997-1999)[1,2]



N = 736.

1. ACCESS Research Group. *J Clin Epidemiol*. 1999;52:1173-1186. **2.** Baughman RP et al. *Am J Respir Crit Care Med.* 2001;164:1885-1889.

Patients With Sarcoidosis May Present With Diverse Symptoms

Pulmonary[1,2]	Systemic[1,2]	Extrapulmonary[1,2]
Dyspnea	Fatigue	Erythema nodosum
Cough and wheezing	Night sweats	Anterior uveitis
Bronchial hyperreactivity	Weight loss	Cranial nerve palsy
Bilateral hilar adenopathy		Hypercalciuria
Fibrosis		Cardiomyopathy
Pulmonary hypertension		

At least one-third of patients are asymptomatic[3]

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2156. **2.** Criado E et al. *Radiographics*. 2010;30:1567-1586. **3.** Baughman RP, Lower EE. *Eur Respir Mon*. 2005;32:301-315.

Some Clinical Features May Be Helpful for Assessing the Likelihood of Sarcoidosis

More Probable	Less Probable
African American or Northern European[1,2] Aged 20-39 years (males and females); aged > 40-50 years in females[3,4a]	Aged <18 years[1,2] Aged >50 years in males[1]
Increased age[1,2]	Exposure to beryllium and other metal dusts[1,2]
Nonsmoker[1]	Exposure to tuberculosis[1,2]
Asymptomatic presentation (especially with consistent radiographic findings)[1,2]	Recurrent infections[2]
Hypergammaglobulinemia[2]	Hypogammaglobulinemia[2]
Peripheral blood lymphopenia[2]	Systemic disease capable of inducing granulomatous reactions[2] ▪ Malignancy ▪ Inflammatory bowel disease ▪ Immunodeficiency
Elevation of liver enzymes or serum calcium[2]	Rales[2] Clubbing[2]
Family history of sarcoidosis[1,2]	
Elevated biomarkers (sIL2R, ACE, 1,25-$(OH)_2$-vitamin D, CD4, lysozymes)1,2	
Multiorgan disease[1,2]	Single organ disease[2]
Radiographic findings including: bilateral hilar adenopathy (especially if without symptoms); HRCT: disease along the bronchovascular bundle; PET/CT Scan[2]	

ACE = angiotensin-converting enzyme; HRCT = high-resolution computed tomography; sIL2R = soluble interleukin 2 receptor.

[a] Studies in northern Europe and Japan have described a bimodal pattern of age-specific incidence among women.[3,4]

1. Judson MA. *Clin Chest Med*. 2008;29:415-427. **2.** Culver DA. *Curr Opin Pulm Med*. 2015;21:499-509. **3.** Dumas O et al. *Ann Am Thorac Soc*. 2016;13:67-71. **4.** Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165.

Lung and Lymph Node Involvement Can Be Detected by Chest Radiography[1-3]

Stage[1,2]	Radiologic Abnormalities	Stage at Diagnosis, %
0	None	5-10
I	Bilateral hilar lymphadenopathy without infiltration	50
II	Bilateral hilar lymphadenopathy with infiltration	25-30
III	Infiltration alone	10-12
IV	Fibrotic bands, bullae, hilar retraction, bronchiectasis, diaphragmatic tenting	5 (up to 25 over disease course)

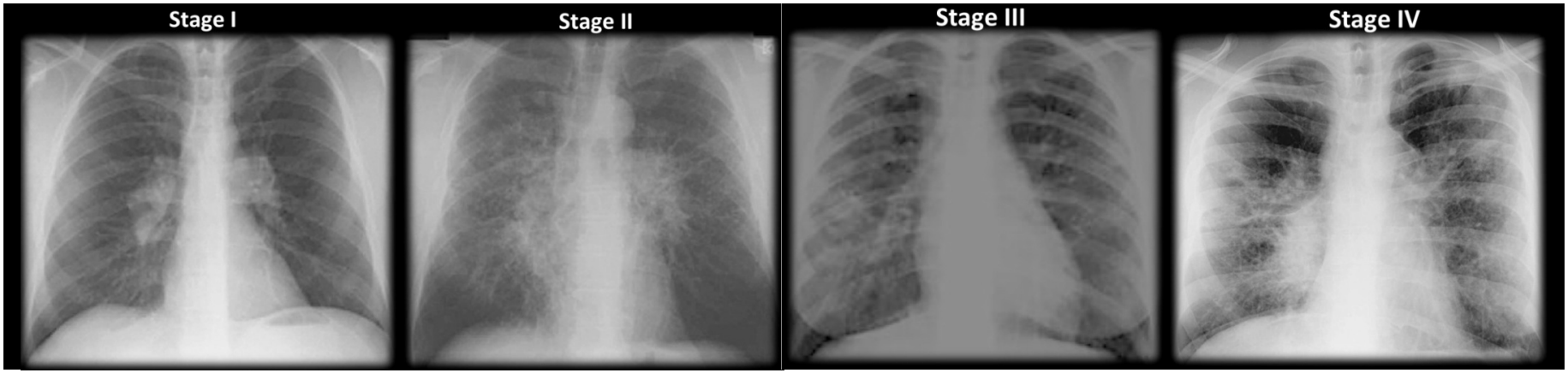
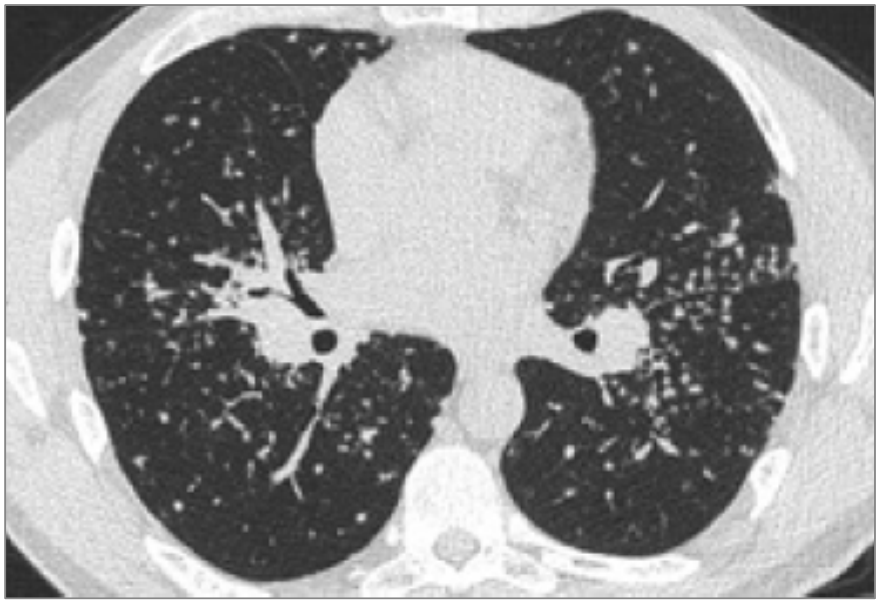


Image reproduced with permission from Jara-Palomares L et al. Clinical manifestations of sarcoidosis. In: Eishi Y, ed. *Sarcoidosis*. London, UK: Intech Open; 2013:109-143.

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165. **2.** Criado E et al. *Radiographics*. 2010;30:1567-1586. **3.** Jara-Palomares L et al. Clinical manifestations of sarcoidosis. In: Eishi Y, ed. *Sarcoidosis*. London, UK: Intech Open; 2013:109-143.

Some Chest CT Features Are Relatively Specific for Pulmonary Sarcoidosis[1]

Bilateral Hilar Adenopathy and/or Perilymphatic Micronodules[1,2]



CT scan depicting bilateral hilar lymphadenopathy and micronodules with a perilymphatic distribution, including spreading along the fissures.

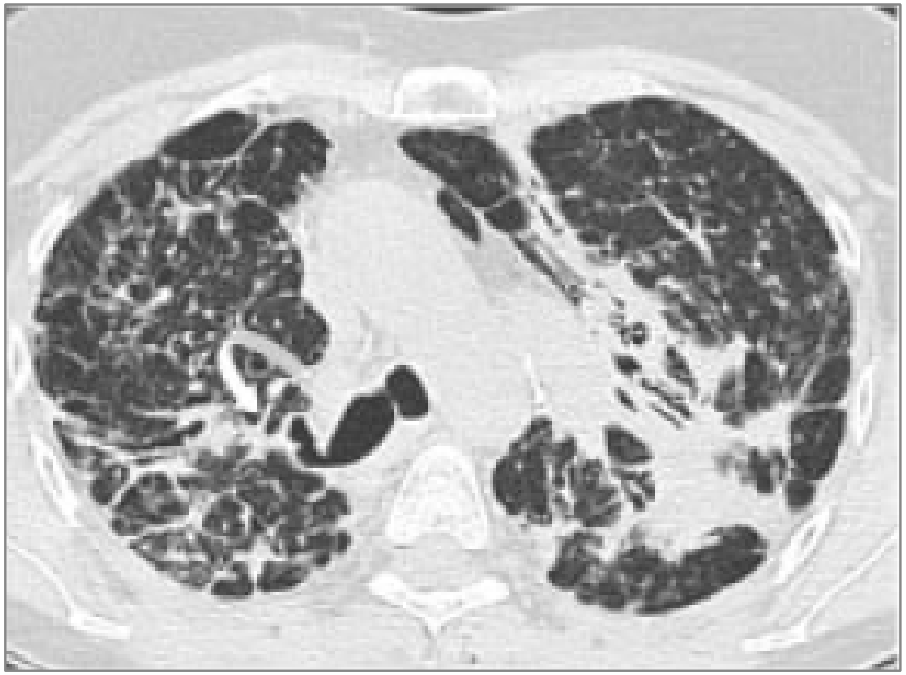
CT = computed tomography.

Image reproduced with permission from Nunes et al. *Eur Respir J*. 2012;40:750.

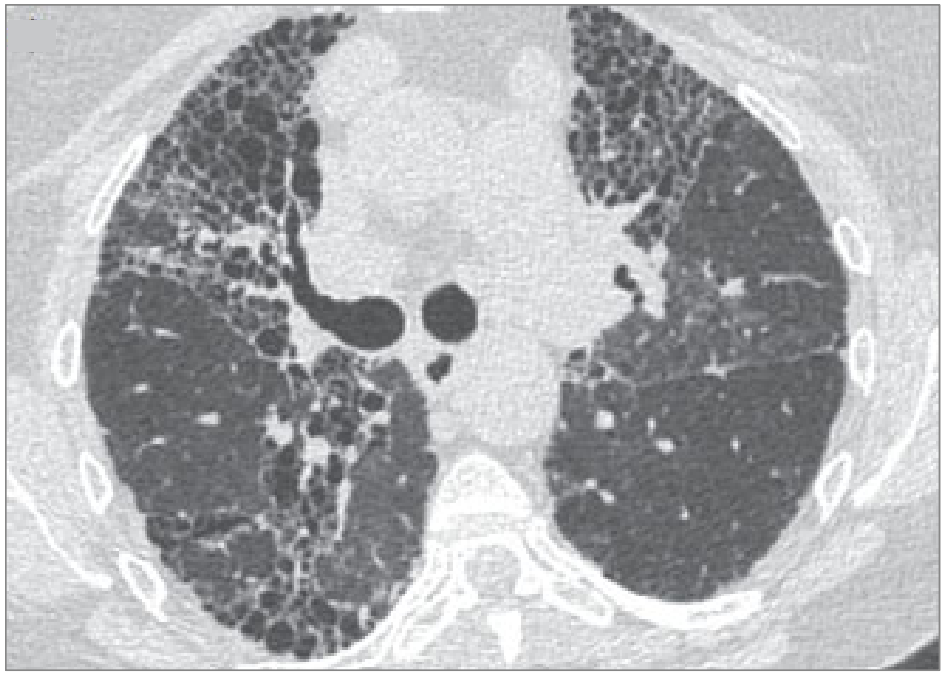
1. Criado E et al. *Radiographics*. 2010;30:1567-1586. **2.** Nunes et al. *Eur Respir J*. 2012;40:750.

Some Chest CT Features Are Relatively Specific for Pulmonary Sarcoidosis[1] (cont'd)

Fibrosis With Honeycombing[2,3]



High-resolution chest CT scan demonstrating fibrotic conglomerate mass in the upper left lobe with traction bronchiectasis



CT scan demonstrating HC, predominantly in the upper and prehilar regions and along the bronchovascular bundles

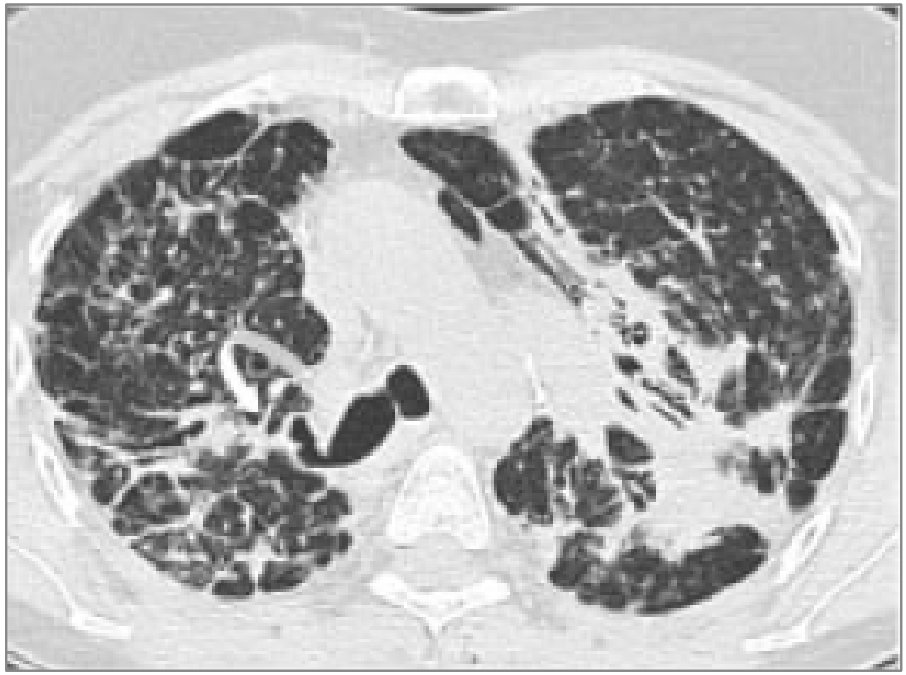
CT = computed tomography; HC = honeycombing.

Images reproduced with permission from Valeyre et al. *Semin Respir Crit Care Med*. 2014;35:336, and Nunes et al. *Eur Respir J*. 2012;40:750.

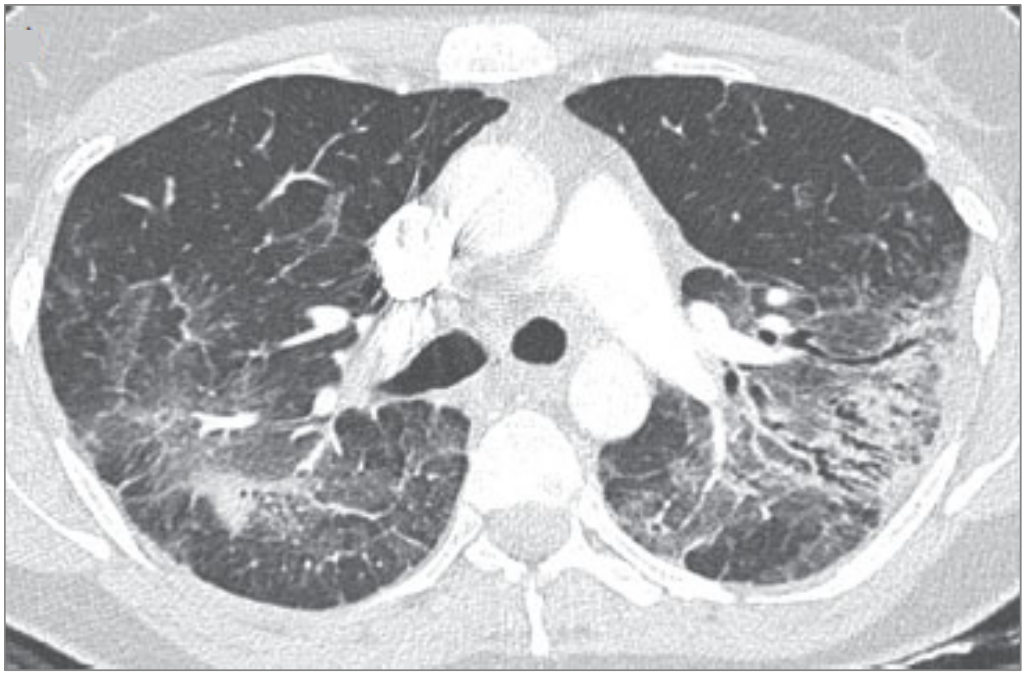
1. Culver DA. *Curr Opin Pulm Med*. 2015,21:499–509. **2.** Valeyre et al. *Semin Respir Crit Care Med*. 2014;35:336. **3.** Nunes et al. *Eur Respir J*. 2012;40:750.

Some Chest CT Features Are Relatively Specific for Pulmonary Sarcoidosis[1] (cont'd)

Fibrosis With Bronchial Distortion[2,3]



High-resolution chest CT scan demonstrating fibrotic conglomerate mass in the upper left lobe with traction bronchiectasis

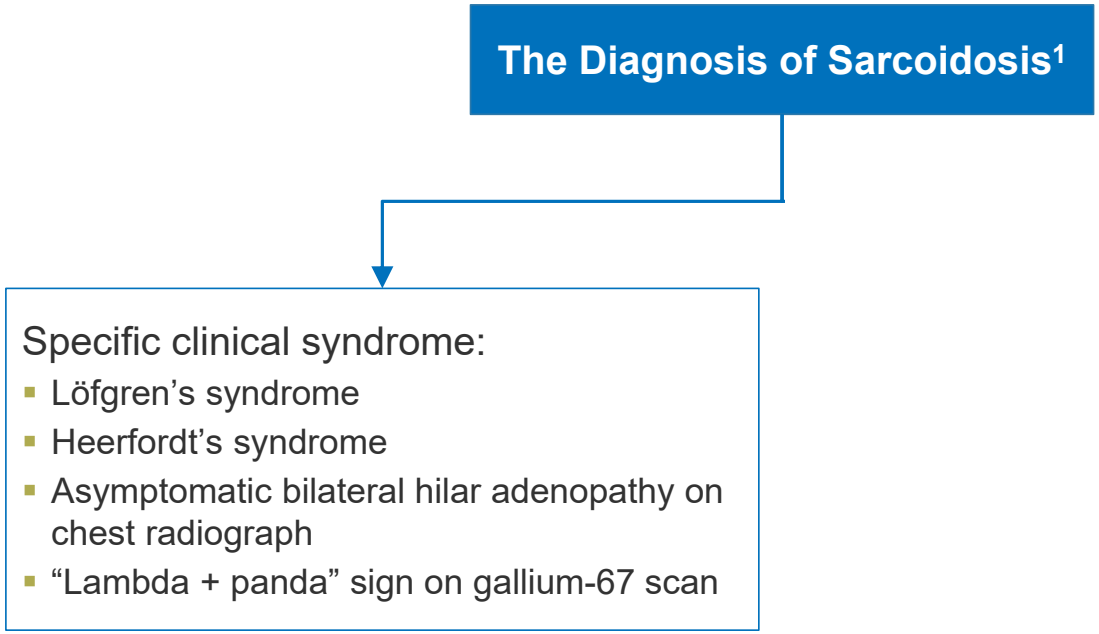


CT scan showing bronchial distortion in the superior and posterior regions

Images reproduced with permission from Valeyre et al. *Semin Respir Crit Care Med*. 2014;35:336, and Nunes et al. *Eur Respir J*. 2012;40:750.

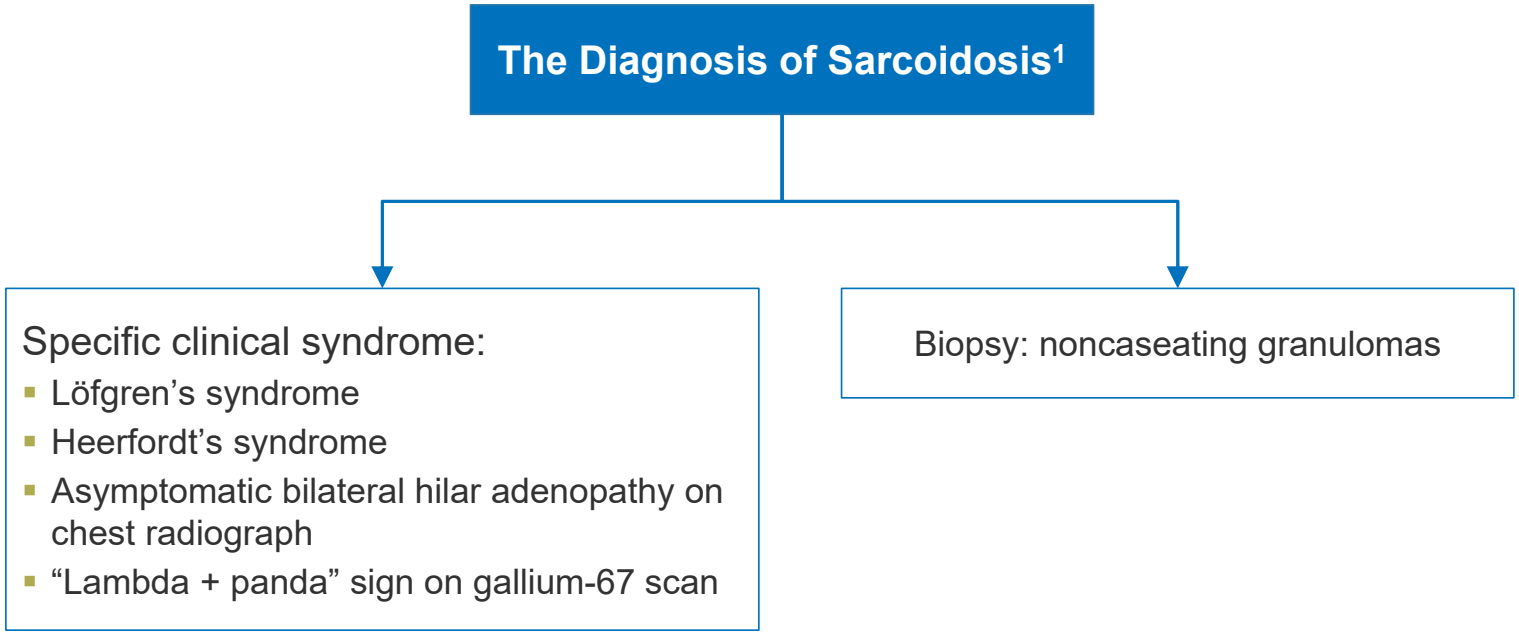
1. Culver DA. *Curr Opin Pulm Med*. 2015,21:499–509. **2.** Valeyre et al. *Semin Respir Crit Care Med*. 2014;35:336. **3.** Nunes et al. *Eur Respir J*. 2012;40:750.

A Probable Diagnosis May Be Made in Patients Who Present With Clinical Findings That Are Specific for Sarcoidosis[1,2]



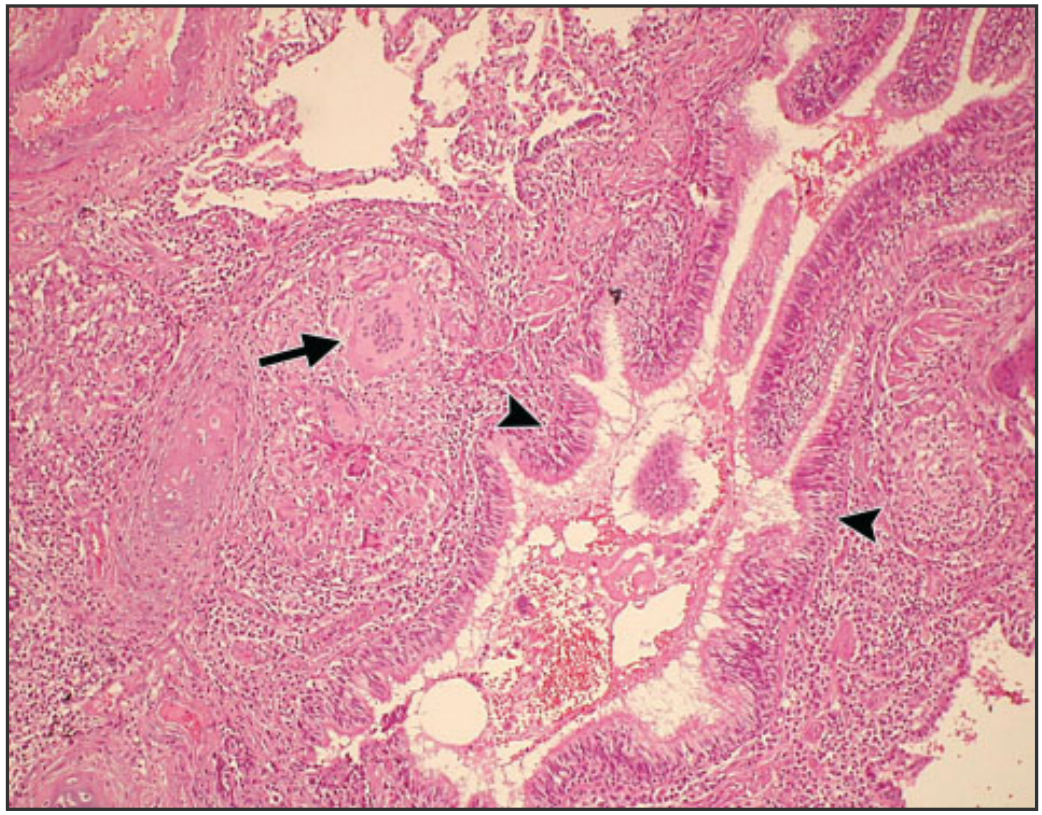
1. Judson MA. *F1000Prime Rep*. 2014;6:89; **2.** Birnie DH et al. *Heart Rhythm.* 2014;11:1305-1323.

A Probable Diagnosis May Be Made in Patients Who Present With Clinical Findings That Are Specific for Sarcoidosis[1,2]



1. Judson MA. *F1000Prime Rep*. 2014;6:89. **2.** Birnie DH et al. *Heart Rhythm.* 2014;11:1305-1323.

Confirmation of Sarcoidosis Requires Histologic Evidence of Noncaseating Granulomas[1,2]



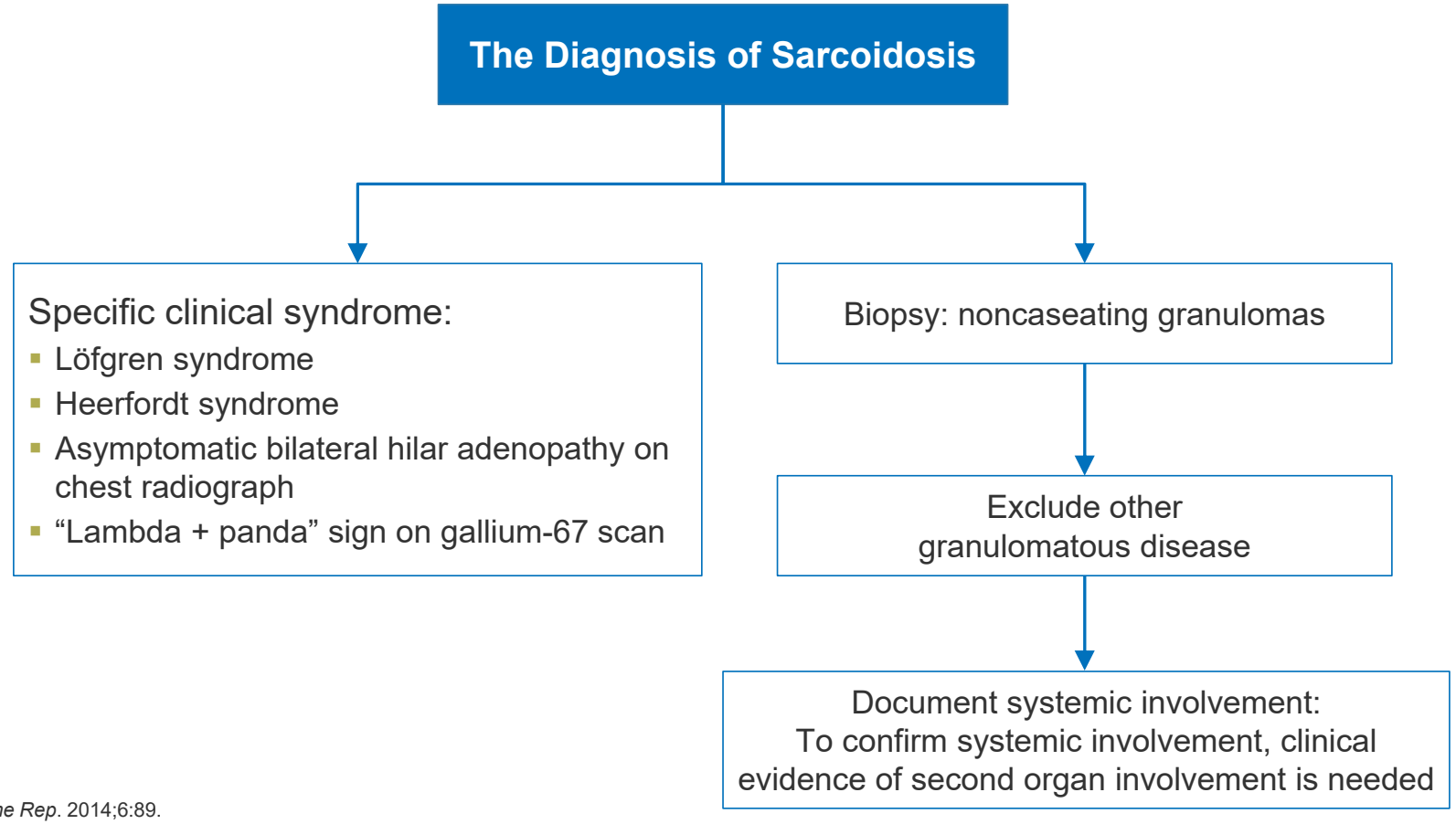
Biopsy should be used to exclude alternate causes of granulomatous inflammation[1]

Lung biopsy: epithelioid granulomas (arrow) surrounding bronchial walls immediately beneath normal bronchial epithelium (arrowheads)[2]

Images reproduced with permission from Criado E et al.

1. Judson MA. *F1000Prime Rep*. 2014;6:89. **2.** Criado E et al. *Radiographics*. 2010;30:1567-1586.

Granulomatous Inflammation, by Itself, Is Insufficient to Establish a Diagnosis of Systemic Sarcoidosis



Judson MA. *F1000Prime Rep*. 2014;6:89.

Serologic Biomarkers May Be Important for the Development of Granulomas or Fibrosis

- Serologic biomarkers are thought to be important in the formation, resolution or potentiation of the sarcoid granuloma
  - Alternatively, may be associated with the development or protection against fibrosis development and other sarcoidosis complications

Clinical Utility of Various Serum Biomarkers of Sarcoidosis

Biomarker	Activity of Biomarker	Diagnostic Utility	Prognostic Utility	Disease Activity Monitoring Utility
SACE	Granuloma burden	+[a]	–	++
sIL-2R	CD4+ T-helper cell activation	–	+	++
Chitotriosidase	Activated macrophages and neutrophils	–	–	++
Chemokines (CXCL9, 10, 11)	Presence of CD4+ T helper Th1 cells	–	+	+
Lysozyme	Activated macrophages and epithelioid cells	–	–	+
KL-6	Lymphocytic alveolitis	–	+	+
Vitamin D dysregulation[b]	Activated macrophages	–	–	+
SAA	Activated macrophages	+[c]	–	+

+ = positive; - = negative; CXCL = (C-X-C motif) ligand; KL-6 = Krebs von del Lungen-6; OH = hydroxide; PTH = parathyroid hormone; SACE = serum angiotensin converting enzyme; sIL-2R = soluble interleukin-2 receptor; SAA = serum amyloid A; ULN = upper limit of normal.

[a] The diagnosis is strongly suggested if values > 2 × ULN.

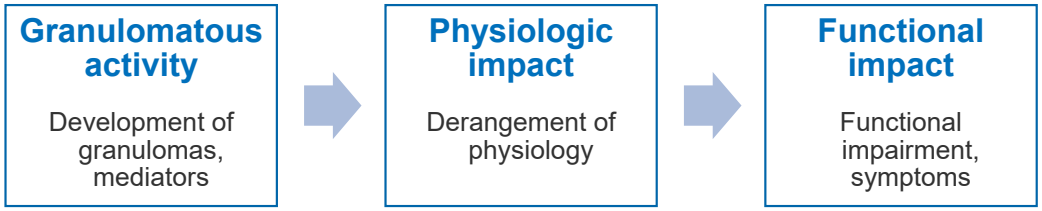
[b] Serum 25-OH vitamin D, 1,25-di-OH vitamin D, PTH.

[c] May be a very specific diagnostic biomarker if identified in tissues via staining.

Chopra A et al. *Expert Rev Clin Immunol*. 2016;12(11):1191-1208.

Biomarkers and Imaging Are Used for Clinical Decisions

- Many techniques, such as biomarker identification and imaging, can support or discourage specific clinical decisions, but should not be used in isolation



Biomarkers

- Clinical data and biomarkers can play a role in management.
- No gold-standard biomarker criteria exist for the diagnosis of sarcoidosis.
- Unidimensional biomarkers are unlikely to encompass the true extent of the disease.
- Many biomarkers that assess disease activity are not useful as a basis for treatment decisions since there is often a poor correlation between the objective measures of sarcoidosis disease activity, disease severity and the patient's QOL.

Imaging

- Provides detail on specific organ involvement
- Radiography and CT can detect granuloma conglomerations; x-rays are the most researched imaging modality.
- ^{18}F-FDG-PET can indicate tissues with active sarcoidosis and is particularly useful for pulmonary and cardiac sarcoidosis.
- MRI is useful for cardiac sarcoidosis and neurosarcoidosis.

^{18}F-FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging.

Chopra A et al. *Expert Rev Clin Immunol*. 2016;12(11):1191-1208.

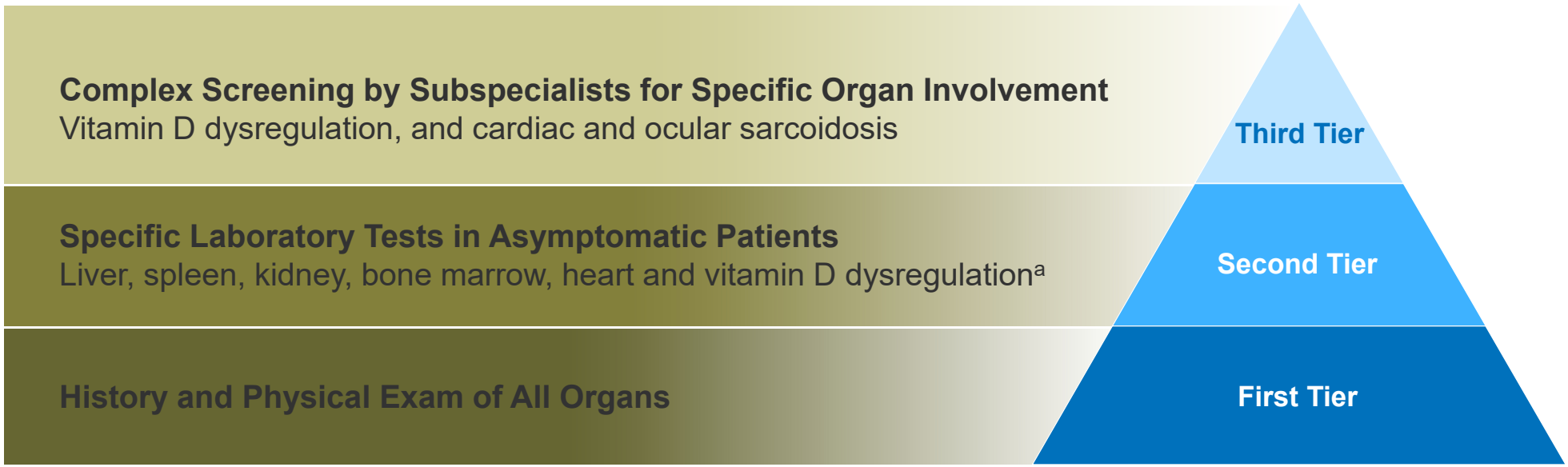
Specific Factors for Lung Involvement

Major Clinical Factors for Pulmonary Sarcoidosis[1,2]

Factor	Finding	Diagnostic Utility	Prognostic Outcome[a]	Disease Activity Monitoring[a]
CXR	Scadding stage 1		Good	
	Scadding stage 1, no symptoms	✓[b]		
	Scadding stage 4		Poor	
HRCT	Perilymphatic nodules	✓[b]		✓[b]
	Galaxy sign	✓[b]		✓[b]
^{18}F-FDG-PET	FDG uptake		Poor	✓[c]
FVC	< 1.5 L		Poor	
DLCO	< 60% predicted	✓[d]		
BAL	Lymphocytosis			✓[c]
	CD4:CD8 > 3.0	✓[b]		✓[c]
	TNF-α elevated		Poor	

BAL = bronchoalveolar lavage; CXR = chest radiograph; DLCO = single breath diffusing capacity for carbon monoxide; FVC = forced vital capacity; HRCT = high-resolution chest computed tomography.
[a] Assumes the diagnosis of sarcoidosis has been established. [b] Specific (true negative rate). [c] Sensitive (true positive rate).[d] Sensitive for pulmonary hypertension.
1. Chopra A et al. *Expert Rev Clin Immunol*. 2016;12(11):1191-1208. **2.** Mostard RLM et al. *Curr Opin Pulm Med*. 2013;19(5):538-544.

Screening for Sarcoidosis Involvement Is Required to Detect Clinically Relevant Multi-Organ Involvement



Patients with sarcoidosis should be routinely screened for any new signs or symptoms that suggest new organ involvement

[a] Assessment of kidney, liver and spleen function as well as bone health.

Judson MA. *Respir Med*. 2016;113:42-49.

First Tier: History and Physical Exam of All Organs

- Any symptom may represent a manifestation of sarcoidosis, because sarcoidosis may affect any organ in the body.
- Temporal presentation of symptoms may be useful in determining if they are likely to be related to sarcoidosis.
- Parasarcoidosis is a syndrome in patients with sarcoidosis causing symptoms and/or dysfunction not directly related to deposition of sarcoid granulomas.
  - May result from systemic increase of mediators from sarcoid granulomas and may include:
    - Small fiber neuropathy
    - Erythema nodosum
    - Fatigue
    - Pain syndromes
  - May not respond to antigranulomatous therapy

Judson MA. *Respir Med*. 2016;113:42-49.

Second Tier: Specific Laboratory Tests in Asymptomatic Patients

- Screening in asymptomatic patients is not indicated for all organs, because the probability of asymptomatic involvement may be low or detection of involvement may not be beneficial.

Organ	Screening Test(s)	Typical Results Suggesting Sarcoidosis
Liver	Serum liver function tests	Isolated elevation of alkaline phosphate Alkaline phosphates elevated greater than transaminase elevation
	Chest CT scan	Hepatomegaly Liver nodules
Spleen	Complete blood count	Diminished cell lines
	Peripheral smear	Howell-Jolly bodies
	Chest CT scan	Splenomegaly Splenic nodules
Kidney	Serum creatinine,[a] uric acid	Elevated creatinine,[b] elevated proteinuria, hypercalciuria
Bone marrow	Complete blood count	Diminished cell lines

[a] Serum electrolytes and blood urea nitrogen should also be tested.

[b] If renal impairment is present, patients should be evaluated for hypercalcemia and hypercalciuria from vitamin D dysregulation. Other causes unrelated to sarcoidosis should be excluded.

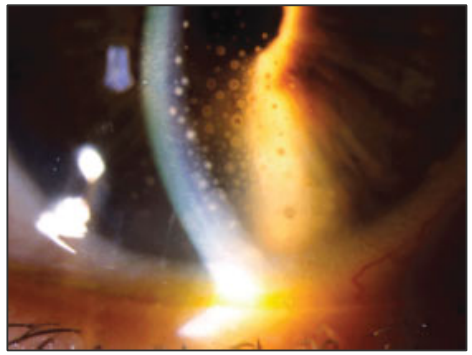
Table adapted with permission from Judson MA.

Judson MA. *Respir Med*. 2016;113:42-49.

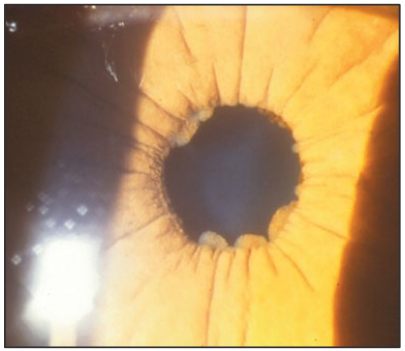
Third Tier: Screening for Ocular Sarcoidosis by an Ophthalmologist

- Many patients may have asymptomatic ocular involvement.[1]
- Exam should include a slit lamp examination, funduscopic examination, conjunctival biopsy, and evaluation of the lacrimal glands.[1,2]

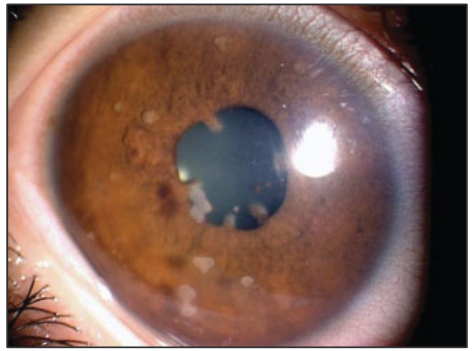
Findings Suggestive of Sarcoidosis[1,a]
Trabecular nodules
Tent-like peripheral anterior synechia
Retinal perivasculitis
Granulomatous iritis ▪ Mutton fat keratic precipitates ▪ Iris nodules
Snowball or string of pearls
Retinochoroidal patchy exudates



Keratic precipitates[2b]



Koeppe nodules[2b]



Busacca nodules[2b]

[a] The presence of any of the first three is highly suggestive of sarcoidosis; the presence of any two is suggestive of sarcoidosis.

[b] Some common manifestations of ocular sarcoidosis.

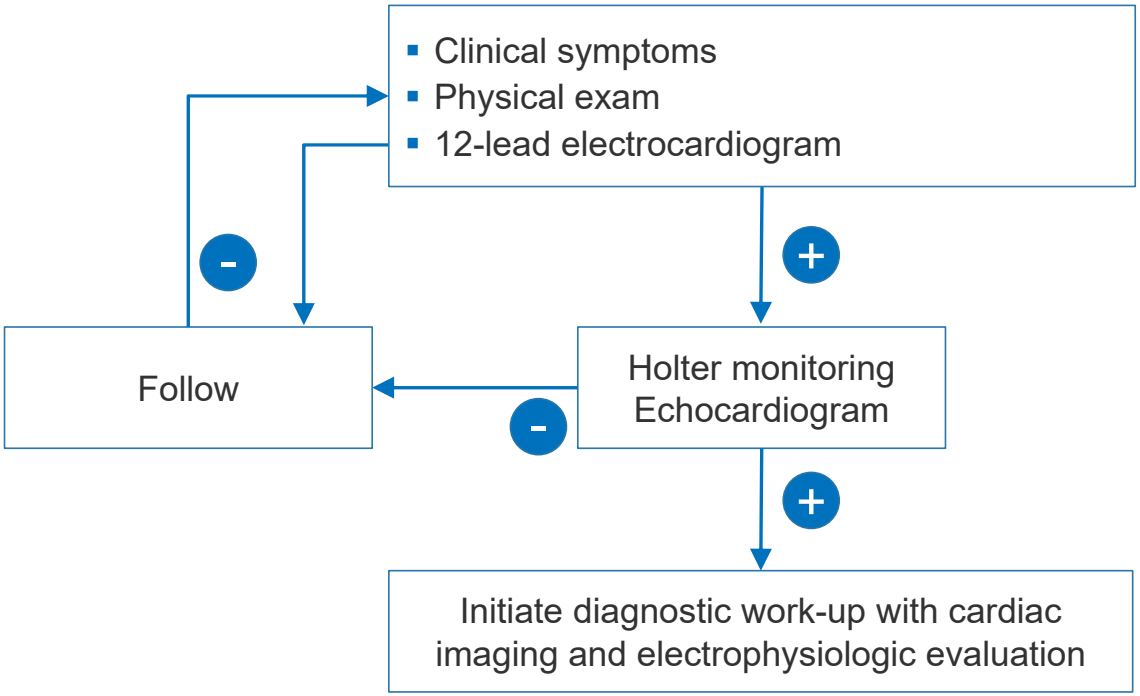
Images reproduced with permission from the publisher (Taylor & Francis Ltd): Herbort CP et al. *Ocul Immunol Inflamm.* 2009;17:160-169.

1. Judson MA. *Respir Med*. 2016;113:42-49. **2.** Herbort CP et al. *Ocul Immunol Inflamm.* 2009;17:160-169.

Third Tier: Screening for Cardiac Sarcoidosis

- Patients should be screened for cardiac involvement, because patients with cardiac sarcoidosis have a poorer prognosis and acute granulomatous inflammation in the heart can suddenly become life-threatening.[1]
- Determining the presence of cardiac symptoms is as important as any single screening test.[1,2]

Routine screening for cardiac sarcoidosis based on a HRS review and a modified Delphi study of sarcoidosis experts[2]



HRS = heart Rhythm Society.

1. Birnie DH et al. *Heart Rhythm.* 2014;11:1305-1323. **2.** Hamzeh N et al. *Chest.* 2012;141:154-162.

Identifying Factors for Survival in Patients With Cardiac Sarcoidosis

- WASOG criteria for cardiac sarcoidosis were recently updated.
- This large cohort study was designed to more thoroughly identify cardiac factors for survival in a cardiac sarcoidosis population using updated criteria.

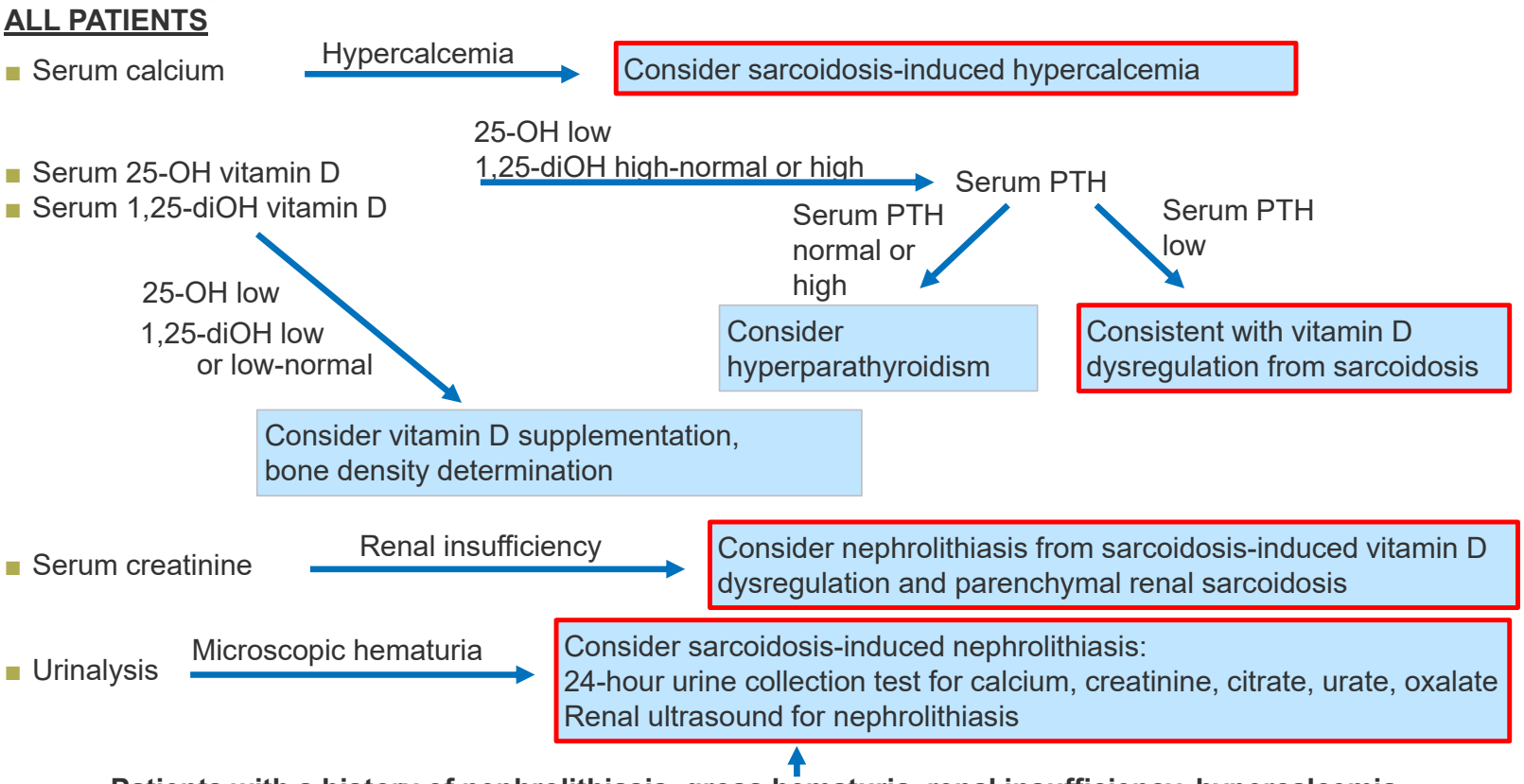
WASOG Criteria[a]	n (%)
Treatment responsive CM or AVNB	12 (16.4)
Reduced LVEF in the absence of other clinical risk factors	40 (54.8)
Spontaneous or inducible sustained VT with no other risk factor	26 (35.6)
Mobitz type II or third-degree heart block	14 (19.2)
Patchy uptake on dedicated cardiac PET scan	23 (31.5)
Positive gallium uptake	1 (1.4)
Defect on perfusion scintigraphy or SPECT scan	0 (0)
T2 prolongation on CMR	1 (1.4)

AVNB = atrioventricular node block; CM = cardiomyopathy; CMR = cardiac MRI; LVEF = left ventricular ejection fraction; SPECT = single-photon emission CT; T2 = T2 (spin-spin) weighted image; VT = ventricular tachycardia; WASOG = World Association of Sarcoidosis and Other Granulomatous Diseases.

[a] Patients could have > one feature.

Zhou Y et al. *Chest*. 2017;151:139-148.

Third Tier: Screening for Vitamin D Dysregulation

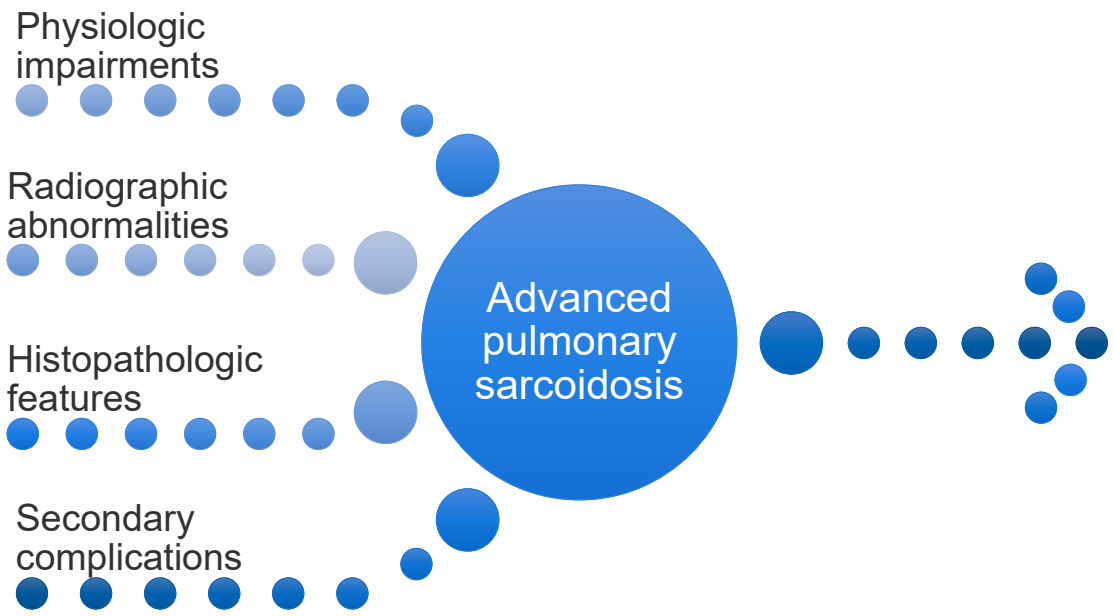


OH = hydroxy; PTH = parathyroid hormone.

Judson MA. *Respir Med*. 2016;113:42-49.

Advanced Pulmonary Sarcoidosis

Advanced Pulmonary Sarcoidosis May Encompass Several Features



Substantial morbidity

Significantly increased mortality risk

Typically difficult to ameliorate

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Advanced Pulmonary Sarcoidosis May Encompass Several Features (cont'd)

Physiologic impairments

- Pulmonary hypertension
- Bronchiectasis
- Airways stenosis
- Mycetoma

Radiographic abnormalities

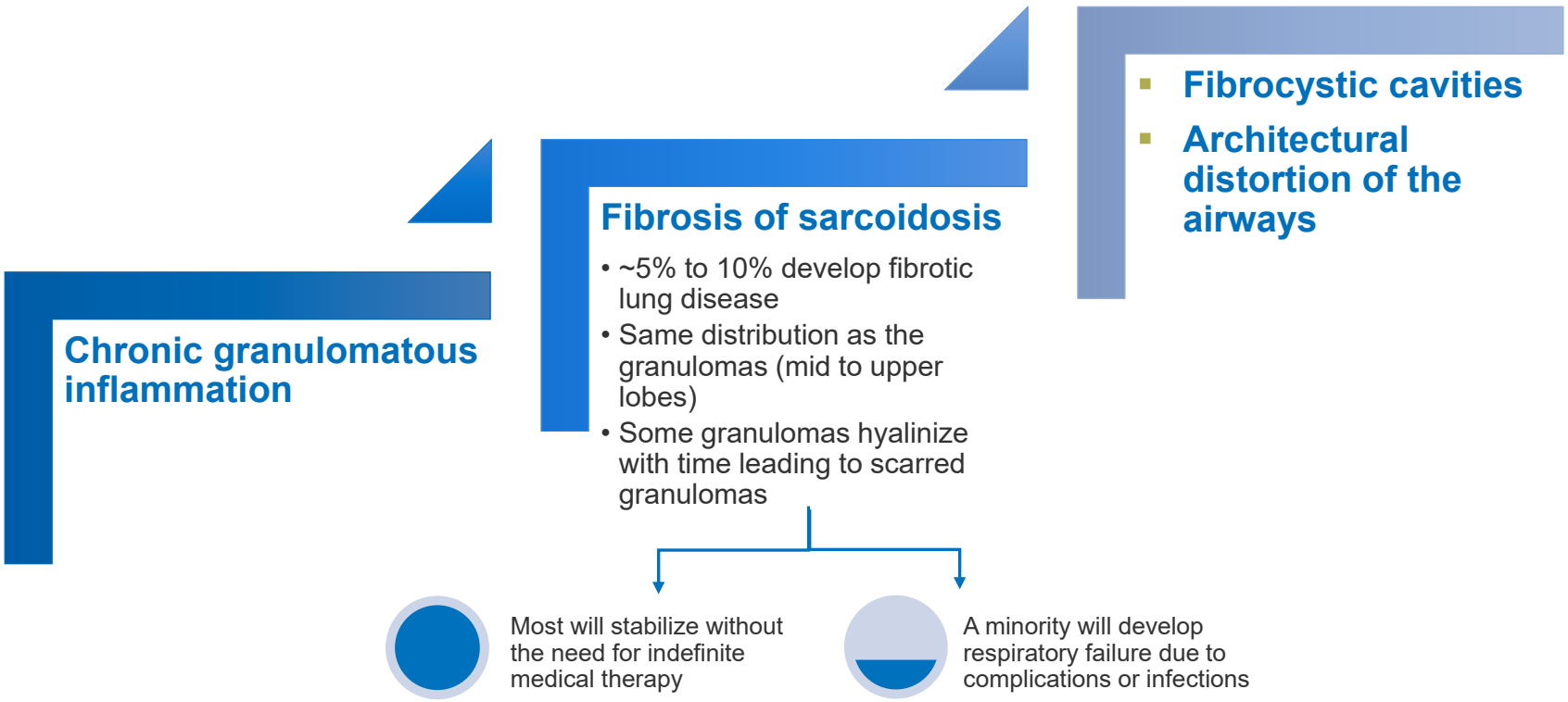
- Predominant fibrotic pattern on chest radiography (ie, Scadding stage 4)

Histopathologic features

- "Fibrotic granulomatous" histopathologic pattern

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Fibrosis Is Observed in Some Patients With Advanced Sarcoidosis



Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Patients With Advanced Pulmonary Sarcoidosis Have Nonspecific and Variable Clinical Presentations

Some common presentations

- Dyspnea
- Cavitary disease (in fibrotic lung disease)
- Obstruction (≤ 75% in patients with fibrotic lung disease)
- Sarcoidosis-associated pulmonary hypertension (≤ 75% in lung transplant candidates)

Some less common presentations

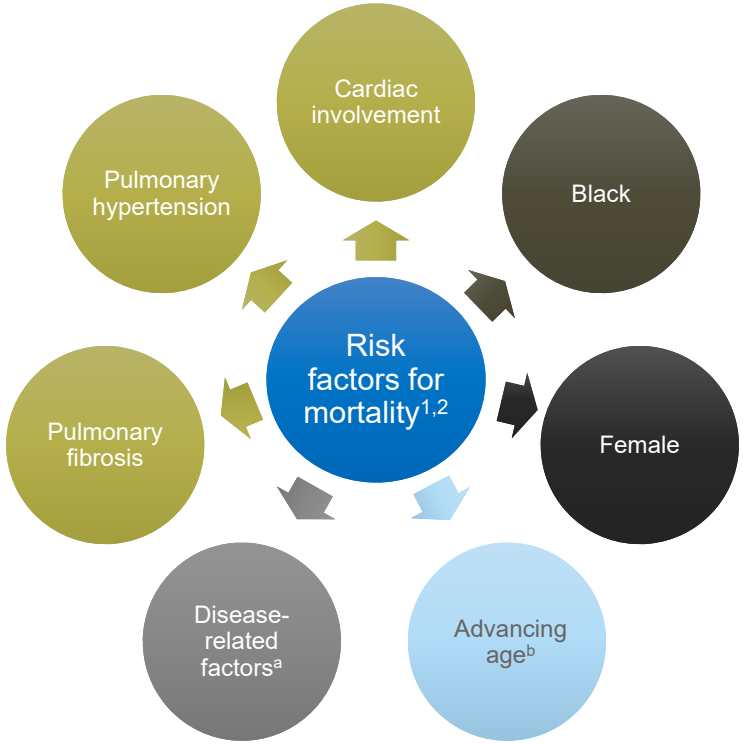
- Bronchiectasis (18% to 40% in stage 4 chest x-rays)
- Crackles (up to 20%)
- Severe airway stenosis (↑ stage 4 chest x-rays)
- Mycetomas arising from secondarily infected pseudocavities (11.3% in stage 4 chest x-rays)
- Hemoptysis (rare but may be seen in patients with mycetomas or endobronchial involvement)

- Some patients with pulmonary fibrosis are asymptomatic and have no functional impairment.

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Advanced Pulmonary Disease and Other Factors Significantly Impact Survival

- Advanced lung disease and its complications have been implicated as the most common cause of death in US patients with sarcoidosis.[1]



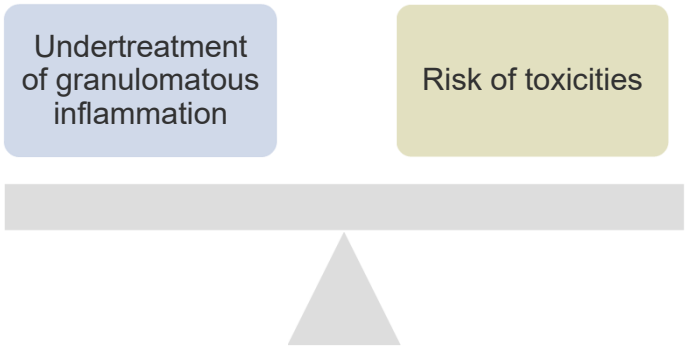
FEV1/FVC = forced expiratory volume in one second over the forced vital capacity; TLC = total lung capacity.

[a] Symptoms at time of diagnosis, radiographic stage 3 or 4 disease, FEV_1/FVC lower ratio, lower FVC, lower FEV_1, lower TLC.

[b] Comorbidities, disease complications or fibrosis development.

1. Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110. **2.** Kirkil G et al. *Chest.* 2018;153:105-113.

Treatment Management Should Balance Risk of Undertreatment With Risk of Toxicity

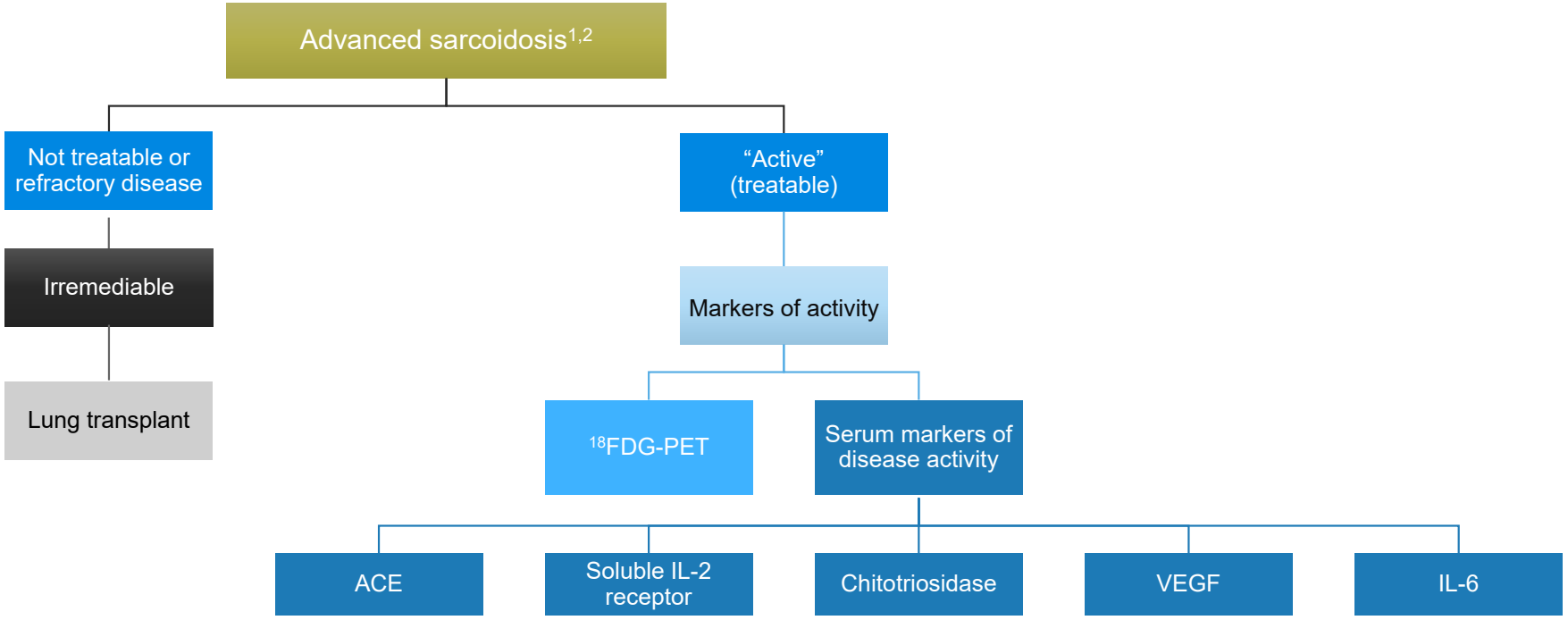


Goal of therapy

- Reduce the burden of granulomatous inflammation with an intention to modify symptoms and decrease functional impairment

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Advanced Sarcoidosis Might Not Equate With Irremediable Disease and Could Potentially Be Treated



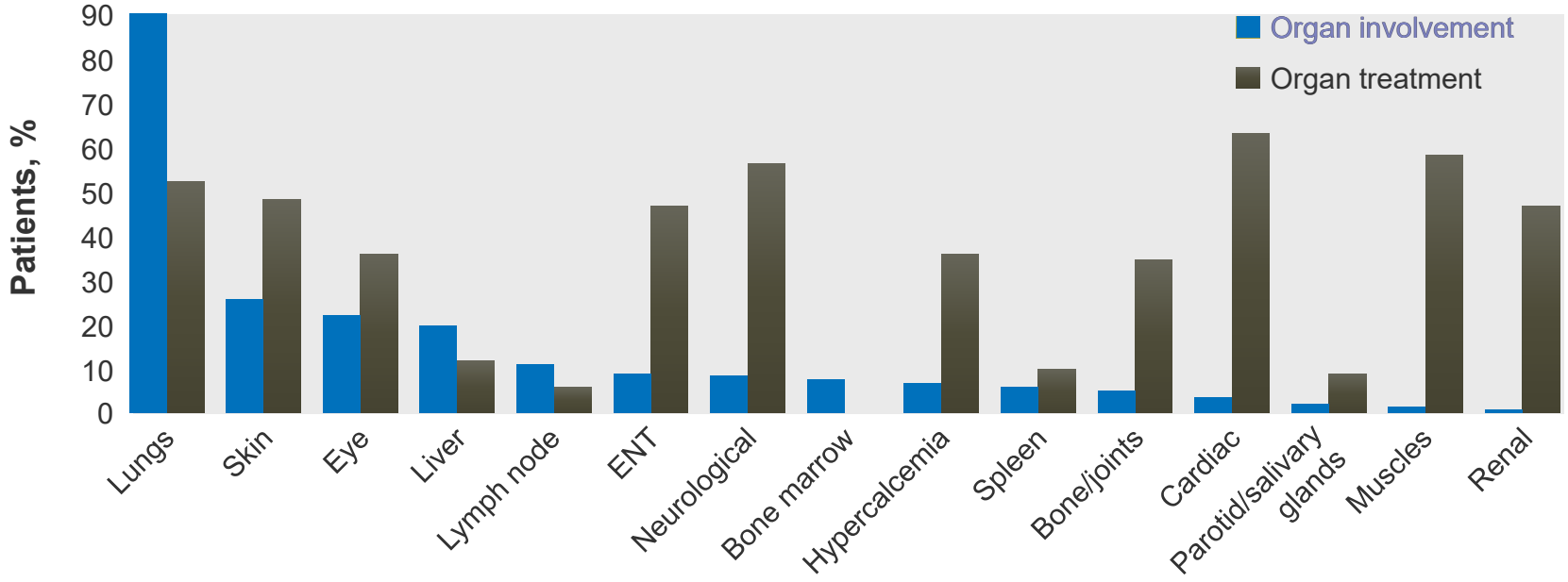
ACE = angiotensin converting enzyme; FDG-PET = ^{18} fluorodeoxyglucose positron emission tomography; IL = interleukin; VEGF = vascular endothelial growth factor.

1. Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110. **2.** Aryal S, Nathan SD. *Ther Adv Respir Dis*. 2019.13:1-15.

Treating Symptomatic Sarcoidosis

Frequency of Organ Involvement and Organs Requiring Treatment in Sarcoidosis

Large, single-cohort, retrospective analysis at the Medical University of South Carolina Multidisciplinary Sarcoidosis Clinic (1999-2010)



ENT = ear, nose and throat.

n = 1582, organ involvement; n = 1043, organ treatment.

Figure adapted with permission from Judson MA et al.

Judson MA et al. *Sarcoidosis Vasc Diffuse Lung Dis.* 2012;29:119-227.

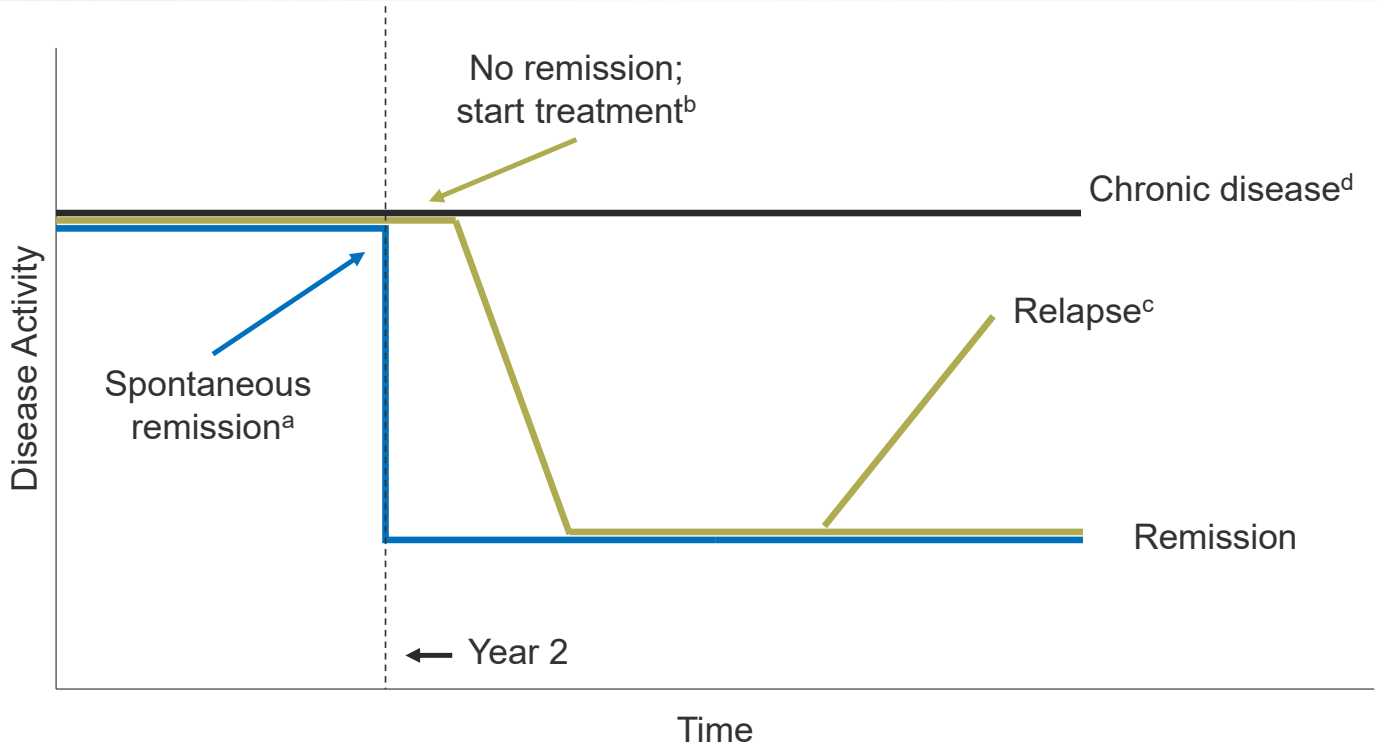
Some Clinical Manifestations Are Associated With a Worse Prognosis

Pulmonary[1]	Extrapulmonary[1,2]	Other[1,2]
Stage III-IV chest radiograph	Cardiac	Age > 40 years at onset
Pulmonary hypertension	Neurologic (except isolated CN palsy)	African American
Significant lung function impairment	Lupus pernio	Requirement for steroids within 6 months of presentation
Moderate to severe dyspnea on presentation	Splenomegaly	
BAL neutrophilia at presentation	Hypercalcemia	
	Osseous disease	

CN = cranial nerve.

1. Lazar CA, Culver DA. *Semin Respir Crit Care Med*. 2010;31:501-518. **2.** American Thoracic Society. *Am J Respir Crit Care Med*. 1999;160:736-755.

Some Cases of Pulmonary Sarcoidosis May Resolve Spontaneously[1,2]



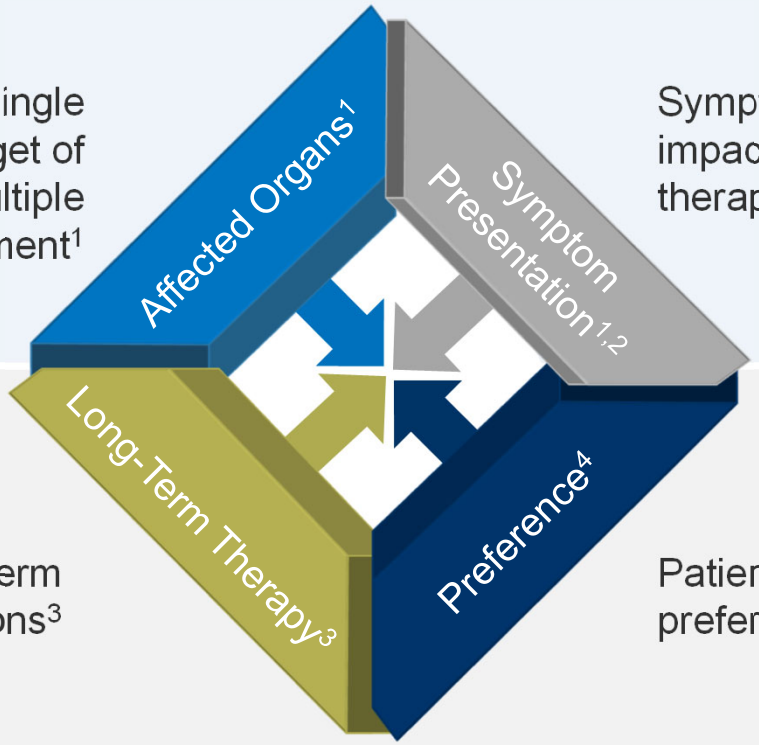
[a] Recent-onset disease has a good prospect for spontaneous remission. Most cases of spontaneous remission occur within the first 2 years of disease. [b] Failure to improve or remit over the first 2 years portended a more difficult course. [c] Relapse occurs more frequently with treatment-induced remission. [d] Up to 30% of patients have chronic disease with long-standing symptom progression or treatment required for > 2 years

1. Lazar CA, Culver DA. *Semin Respir Crit Care Med*. 2010;31:501-518. **2.** Culver DA et al. *Cleve Clin J Med*. 2004;71:88-106.

Choice of Therapy Is Based on a Variety of Factors

The most significant single organ is often the target of therapy, even if multiple organs require treatment[1]

Symptom presentation impacts decision to treat and therapies used[1,2]



Consider long-term toxicities of medications[3]

Patient and physician preference[4]

1. Baughman R et al. *Semin Respir Crit Care Med*. 2014;35:391-406. **2.** Pulmonary, Critical Care, Sleep Update. Sarcoidosis New Concepts in Cause and Treatment. http://www.chestnet.org/Education/eLearning/e-Learning/Sarcoidosis-New-Concepts-in-Cause-and-Treatment Accessed July 10, 2020. **3.** Lazar CA, Culver DA. *Semin Respir Crit Care Med*. 2010;31:501-518. **4.** Baughman RP, Lower EE. *Eur Respir Mon*. 2005;32:301-315.

Immunosuppressants Are Used to Treat Sarcoidosis

- Immunosuppressants are agents that suppress the immune system and are used for the control of pathological immune response in autoimmune disease.[1]

Classification of Immunosuppressants

Mechanism of Action[1]	Biological Effect[1]	Example[1]	Used in Sarcoidosis[2]
Inhibitors of lymphocyte gene expression	Reduce inflammatory response	Glucocorticoids	✓
Inhibitors of lymphocyte signaling	Prevent immune cell activation and proliferation	• Calcineurin inhibitors • mTOR inhibitors	
Cytotoxic agents	Reduce lymphocyte proliferation	• Antimetabolites • Alkylating agents	✓
Cytokine inhibitors	Inhibit proinflammatory or lymphocyte-stimulating cytokines	• TNF-α inhibitors	✓
Anti-immune cell molecule antibodies	Inhibit specific immune cell molecules	Monoclonal or polyclonal antibodies	

mTOR = mechanistic target of rapamycin

1. Reprinted from Patil US et al. *Int J Pharm Pharm Sci.* 2012;4(Suppl 1):30-36. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). **2.** Foundation for Sarcoidosis Research. Physicians' Treatment Protocol. www.stopsarcoidosis.org/wp-content/uploads/FSR-Physicians-Protocol1.pdf. Accessed July 10, 2020.

When Should Immunosuppressive Therapy Be Initiated?

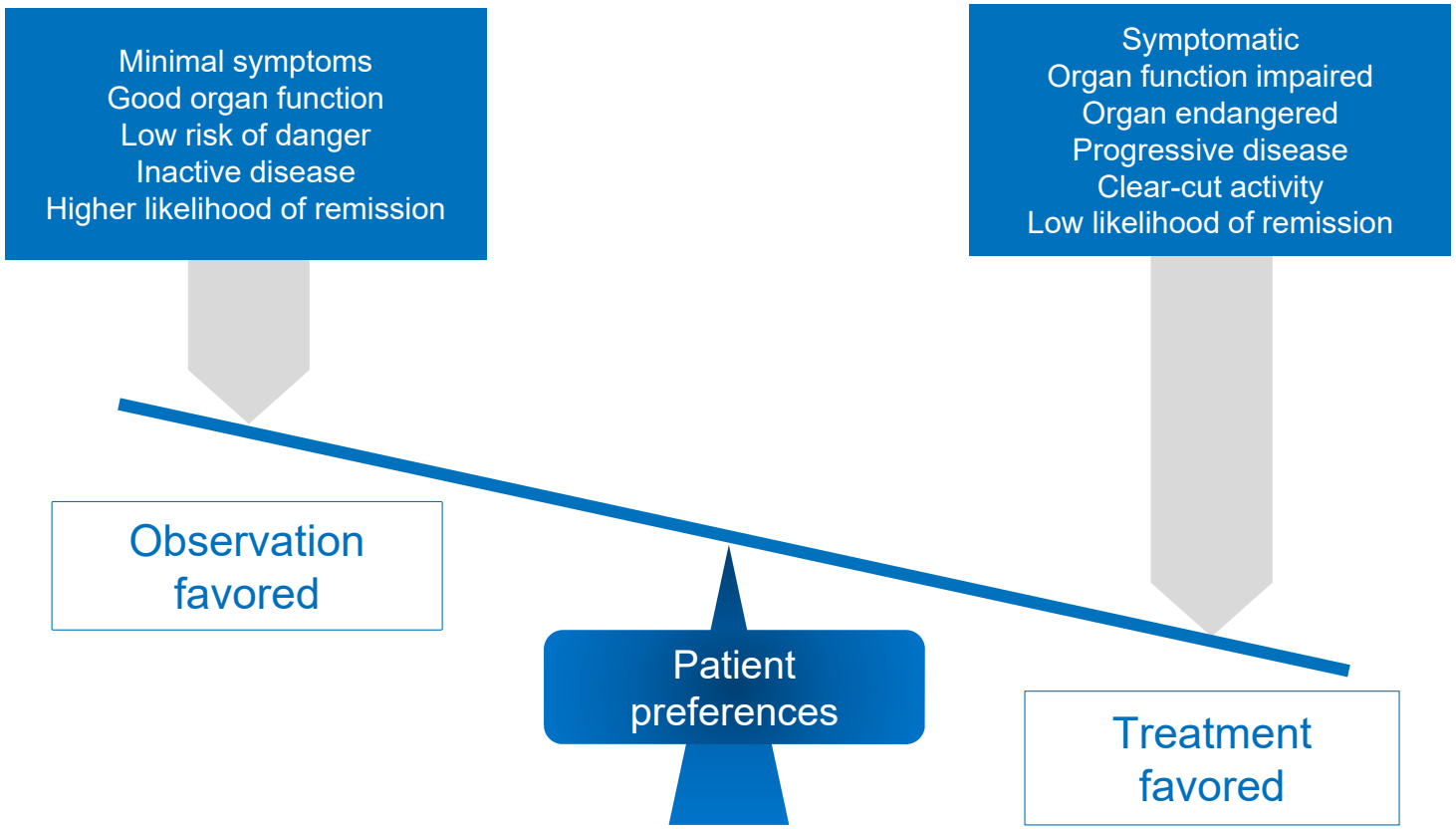


Figure reproduced with permission from Wijsenbeek MS, Culver DA.
Wijsenbeek MS, Culver DA. *Clin Chest Med.* 2015;36:751-767 *Clin Chest Med.* 2015;36:751-767.

Therapies Used for Symptomatic Sarcoidosis: Strength of Recommendation and Level of Evidence

Therapy[1-3]	Grade of Recommendation[a,b]
Biologics	1A, 1B
Corticosteroids	1A
Corticotropin	1C
Cytotoxics	1A, 1B, 1C

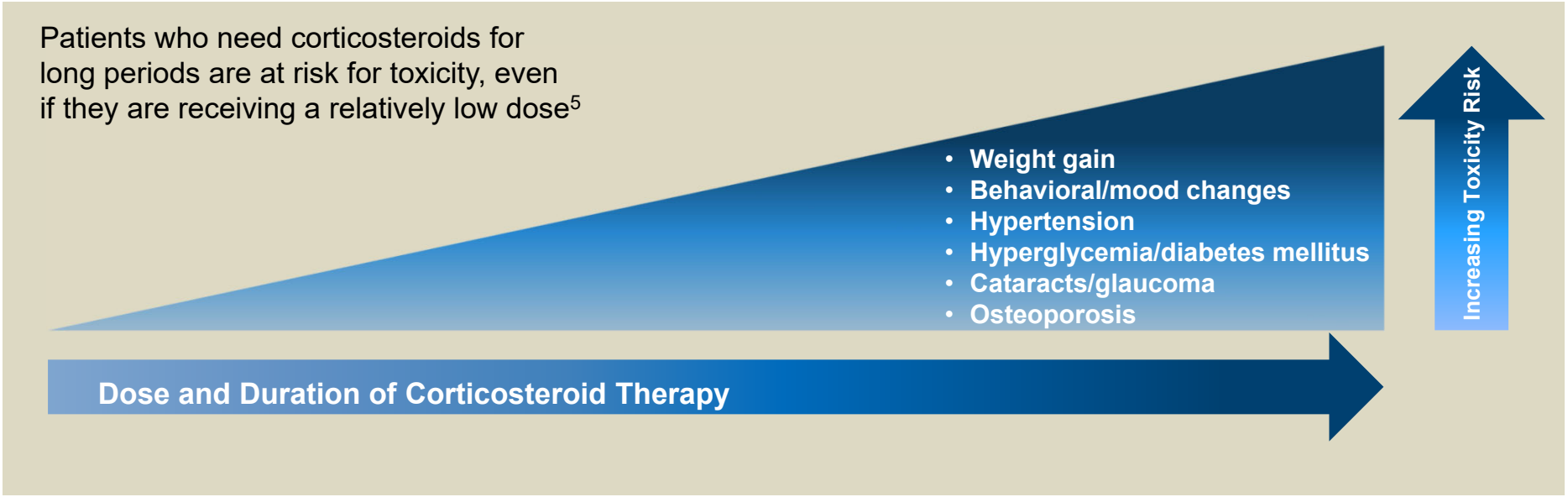
[a] Strength of recommendation: 1, strong recommendation (benefits outweigh risks and burdens, or the reverse); 2, weak recommendation (risks and burdens are finely balanced or magnitude of benefits and risk is uncertain).

[b] Level of evidence: A, high-quality evidence; B, moderate-quality evidence; C, low-quality evidence.

1. Zhou Y et al. *Expert Rev Respir Med.* 2016;10:577-591. **2.** Foundation for Sarcoidosis Research. Physicians' Treatment Protocol. www.stopsarcoidosis.org/wp-content/uploads/FSR-Physicians-Protocol1.pdf. Accessed July 10, 2020. **3.** Guyatt G et al. *Chest*. 2006;129:174.

A Goal of Sarcoidosis Treatment Is to Reduce Toxicity Associated With Corticosteroids

- Corticosteroids are FDA approved for the treatment of patients with symptomatic sarcoidosis.[1-3]
- Corticosteroids are recommended as first-line treatment in the clinical guidelines.[1]
- As with most sarcoidosis therapies, optimal dose and duration of treatment remain unclear.[4]



FDA = US Food and Drug Administration.

1. Foundation for Sarcoidosis Research. Physicians' Treatment Protocol. www.stopsarcoidosis.org/wp-content/uploads/FSR-Physicians-Protocol1.pdf. Accessed July 10, 2020. **2.** Rayos prescribing information, Horizon Pharma USA, Inc. **3.** Orapred ODT prescribing information, Alliant Pharmaceuticals, Inc. **4.** Judson MA. *Chest*. 1999;115:1158-1165. **5.** Beegle et al. *Drug Des Devel Ther*. 2013;7:325.

Steroids or Steroid-Sparing Drugs?

Steroid-sparing agents should be considered for patients who require long-term therapy, have persistent disease or are intolerant to corticosteroids[1,2]

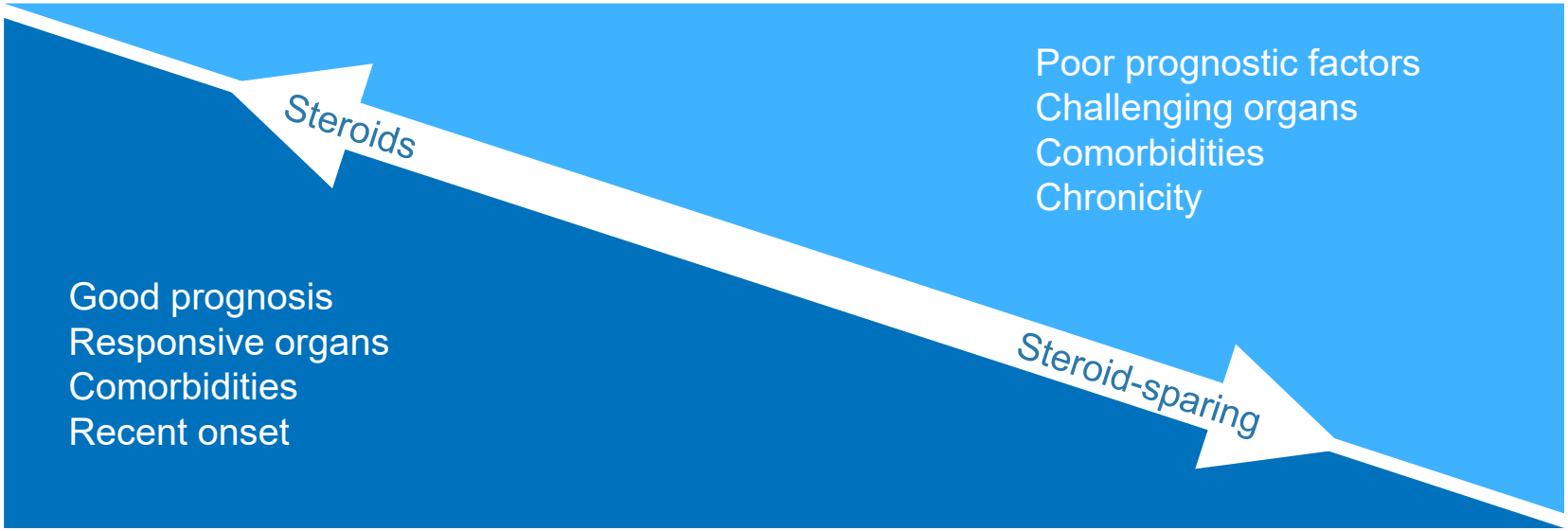
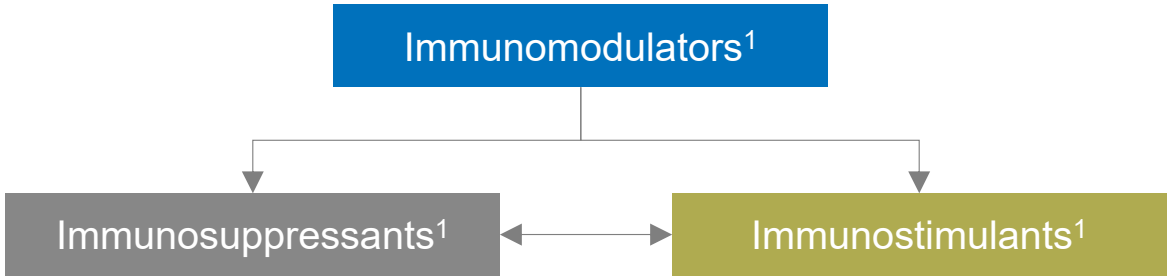


Image reproduced with permission from Wijsenbeek MS, Culver DA. *Clin Chest Med.* 2015;36:751-767.

1. Lazar CA, Culver DA. *Semin Respir Crit Care Med*. 2010;31:501-518. **2.** Wijsenbeek MS, Culver DA. *Clin Chest Med.* 2015;36:751-767.

Immunomodulators May Provide a Novel Approach to the Treatment of Sarcoidosis[1]

- Immunomodulators help the body optimize its immune system.[1]
- Focusing on a single aspect of the immunopathogenesis of sarcoidosis instead of the broad picture could lead to the oversimplification of the immunological process and divert efforts away from other mechanisms.[2]



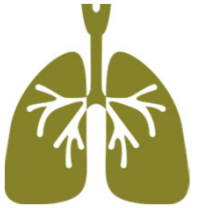
- May restore depressed immune function of lymphocytes, monocytes and macrophages[1]
- May increase cytokine production, leading to increased lymphocyte proliferation or lymphocyte surface marker induction[1]

1. Reprinted from Patil US et al. *Int J Pharm Pharm Sci.* 2012;4(Suppl 1):30-36. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). **2.** Loke WS et al. *Int J Chronic Dis*. 2013;2013:928601.

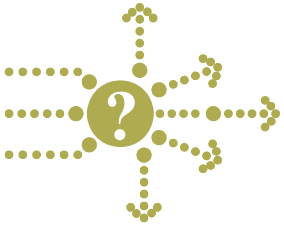
Despite Advances in Sarcoidosis, Unmet Clinical Needs Still Exist

Definitive diagnostic criteria[1]

Clear indicators for treatment and optimal approach[1]

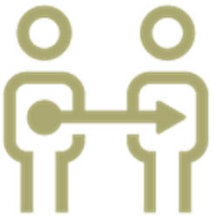


Identification of patients with advanced disease[2]



Elucidation of natural course of the disease[1]

Clinical data on steroid-sparing therapies[1]



Differentiation of advanced disease from irreversible disease[2]

1. Judson MA. *F1000Prime Rep*. 2014;6:89. **2.** Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.

Summary

- Sarcoidosis is a systemic autoimmune disease.[1,2]
  - Involves immune dysregulation
- Pulmonary sarcoidosis is the most common form of the disease, but many patients exhibit both pulmonary and extrapulmonary manifestations.[3]
- There are no definitive diagnostic criteria; diagnosis is established after exclusion of other diseases and compatibility of clinical, radiologic and histologic evidence.[4,5]
- The use of biomarkers and imaging can help support or discourage specific clinical decisions, but should not be used in isolation.[6]
- Up to 30% of patients have chronic disease, with long-standing symptom progression or treatment required for >2 years.[7]
- Immunomodulators may provide an alternative approach to the treatment of sarcoidosis.[8]
- Given the need to identify patients with advanced disease, referral to multidisciplinary centers specializing in sarcoidosis may be considered to optimize patient outcomes.[4,8]

1. Iannuzzi MC et al. *N Engl J Med*. 2007;357:2153-2165. **2.** Broos CE et al. *Front Immunol*. 2013;4:437. **3.** Judson MA et al. *Sarcoidosis Vasc Diffuse Lung Dis*. 2012;29:119-127. **4.** Judson MA. *F1000Prime Rep*. 2014;6:89. **5.** Birnie DH et al. *Heart Rhythm.* 2014;11:1305-1323. **6.** Chopra A et al. *Expert Rev Clin Immunol*. 2016;12(11):1191-1208. **7.** Culver DA et al. *Cleve Clin J Med*. 2004;71:88-106.

Thank you for your attention.

Mallinckrodt Pharmaceuticals

Optional Slides

Multiple Factors Account for Poor HRQOL and Significant Mental Health Symptoms

- Unpredictable multisystemic disease characterized by exacerbations and remissions
- No effective therapy free of significant side effects
- Multiple complaints of fatigue, body pain and low energy difficult to assess and frustrating to manage
- Many patients are reported to have
  - Lower average income
  - Lower perceived access to quality health care
  - Lower satisfaction with health care

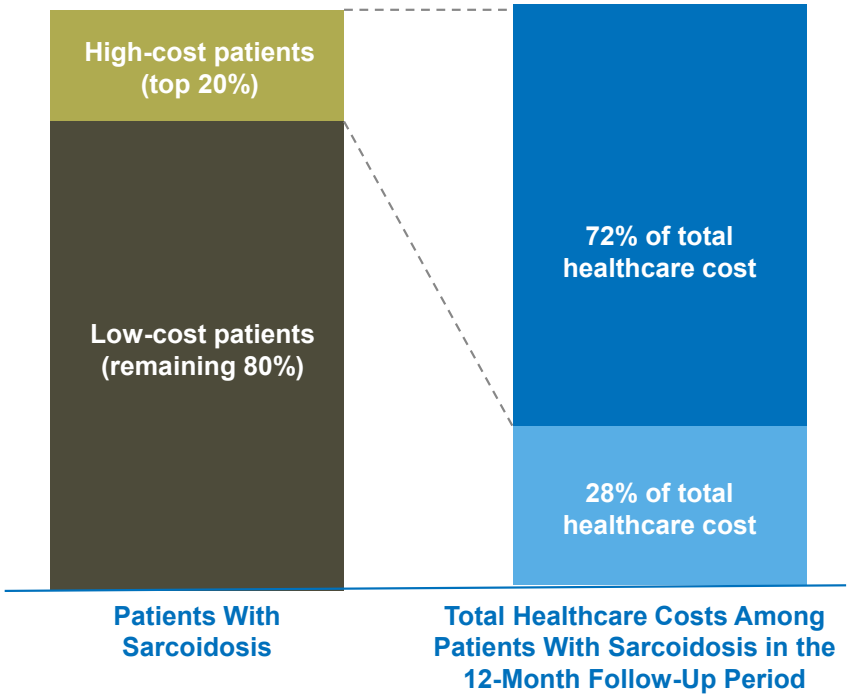
HRQOL = health-related quality of life.

Cox CE et al. *Chest*. 2004;125(3):997-1004.

In Sarcoidosis, 20% of Patients Account for 72% of Total Associated Healthcare Costs

High-cost patients had:

- Higher chronic comorbidity burden
- More sarcoidosis-related comorbidities
  - 46.3% had five or more sarcoidosis-related comorbidities compared with 16.5% of low-cost patients
- Significantly increased rates of comorbidities than low-cost patients:
  - Primary hypertension (54.3% vs 39.4%)
  - Chronic pulmonary disease (42.3% vs 26.3%)
  - Cardiac arrhythmia (28.5% vs 9.2%)
  - Diabetes (28.7% vs 14.7%)
  - Depression (21.1% vs 10.6%)



Rice JB et al. *J Manag Care Spec Pharm*. 2017;23:1261-1269.

Potential Risk Factors for Development of Advanced Disease May Include Those of Persistent or Bothersome Sarcoidosis

Advanced pulmonary sarcoidosis =

Persistent disease

+

Clinically bothersome disease

- Progressive or chronic sarcoidosis do not always lead to advanced disease but represent markers for its development
- Nonresolution of sarcoidosis is a prerequisite for development of advanced disease, but nonresolution alone does not indicate severe disease

- Progressive disease that causes substantial symptoms, impairs QOL or requires treatment

Risk Factors for Persistent and Clinically Bothersome Pulmonary Sarcoidosis

Risk Factors for Persistent Disease	Risk Factors for Clinically Bothersome Disease
Black	Black
Older	More dyspnea at time of diagnosis
Female	Need for treatment during first 6 months after diagnosis
Multiple organ involvement	Multiple organ involvement
Ascending Scadding radiograph stage	Ascending Scadding radiograph stage
Scadding stage at presentation	Lower socioeconomic status
Architectural distortion of the airways or cystic changes	
Absence of lymphadenopathy	
Need for systemic therapy	
Splenomegaly	

QOL = quality of life.

Patel DC, Budev M, and Culver DA. In: Judson MA, ed. *Pulmonary Sarcoidosis, a Guide for the Practicing Physician*. New York, NY: Springer Science+Business Media; 2014:79-110.