aTyr

Sarcoidosis and the Current Landscape Treatment

Key Opinion Leader Webinar

JULY 18, 2019

Forward-Looking Statements

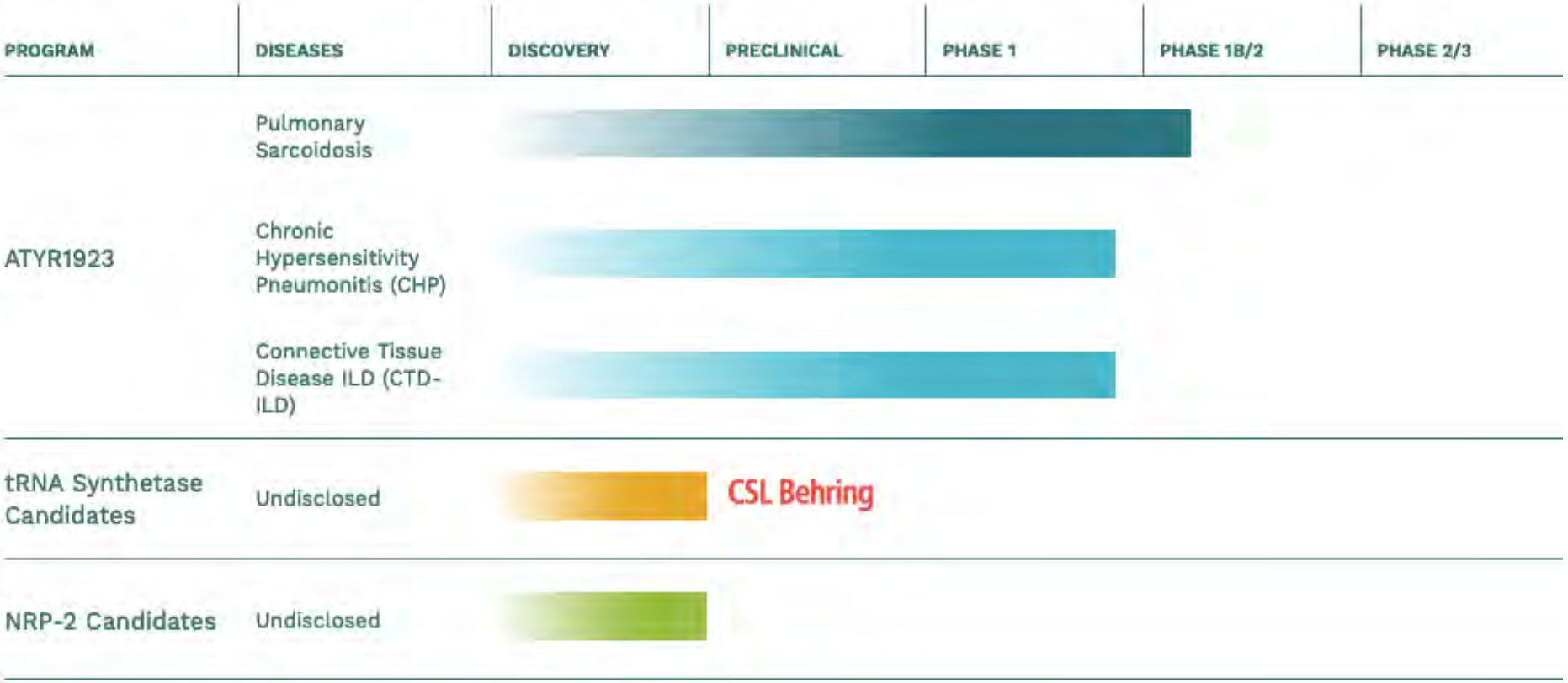
The following slides and any accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” “opportunity,” or “continue,” and other similar expressions are intended to identify forward-looking statements. For example, all statements we make regarding our projected cash expenditures; the potential therapeutic benefits of proteins derived from tRNA synthetase genes and our product candidates, including ATYR1923 and any other product candidates; the ability to successfully advance our product candidates and undertake certain development activities (such as the initiation of clinical trials, clinical trials enrollment, the conduct of clinical trials and announcement of top-line results) and accomplish certain development goals, and the timing of such events; our ability to receive regulatory approvals for, and commercialize, our product candidates; our ability to identify and discover additional product candidates; and the ability of our intellectual property portfolio to provide protection are forward-looking statements. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These risks, uncertainties and other factors are more fully described in our filings with the U.S. Securities and Exchange Commission, including our Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q, and in our other filings. The forward-looking statements in this presentation speak only as of the date of this presentation and neither we nor any other person assume responsibility for the accuracy and completeness of any forward-looking statement. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

aTyr Pharma
Company Overview

Corporate Overview

Founded:	2005 by Paul Schimmel, Ph.D. and Xiang-Lei Yang, Ph.D, leading tRNA synthetase researchers at *The Scripps Research Institute (TSRI)*
Science:	Discovering and developing novel therapeutics based on our understanding of the extracellular functionalities of tRNA synthetase genes
Patents:	Global intellectual property estate directed to a potential pipeline of protein compositions derived from 20 tRNA synthetase genes covering ~300 protein compositions
Located:	San Diego, CA, with subsidiary operations in Hong Kong

Development Pipeline



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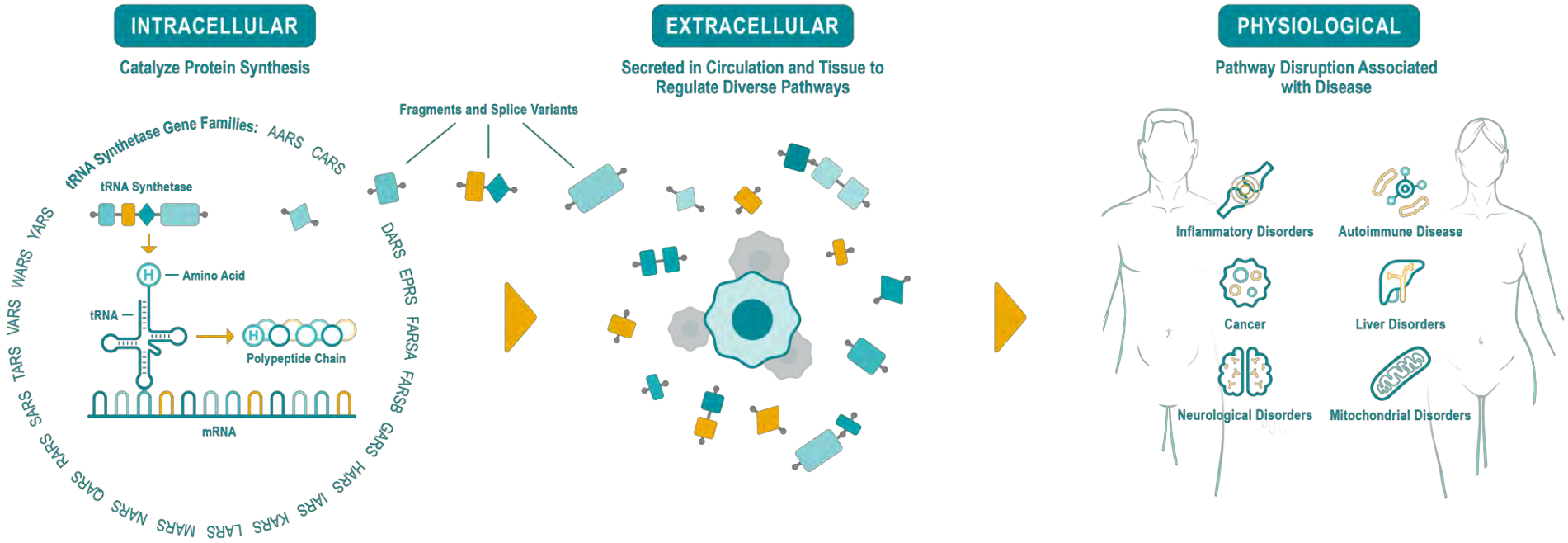
Extracellular tRNA Synthetase Biology



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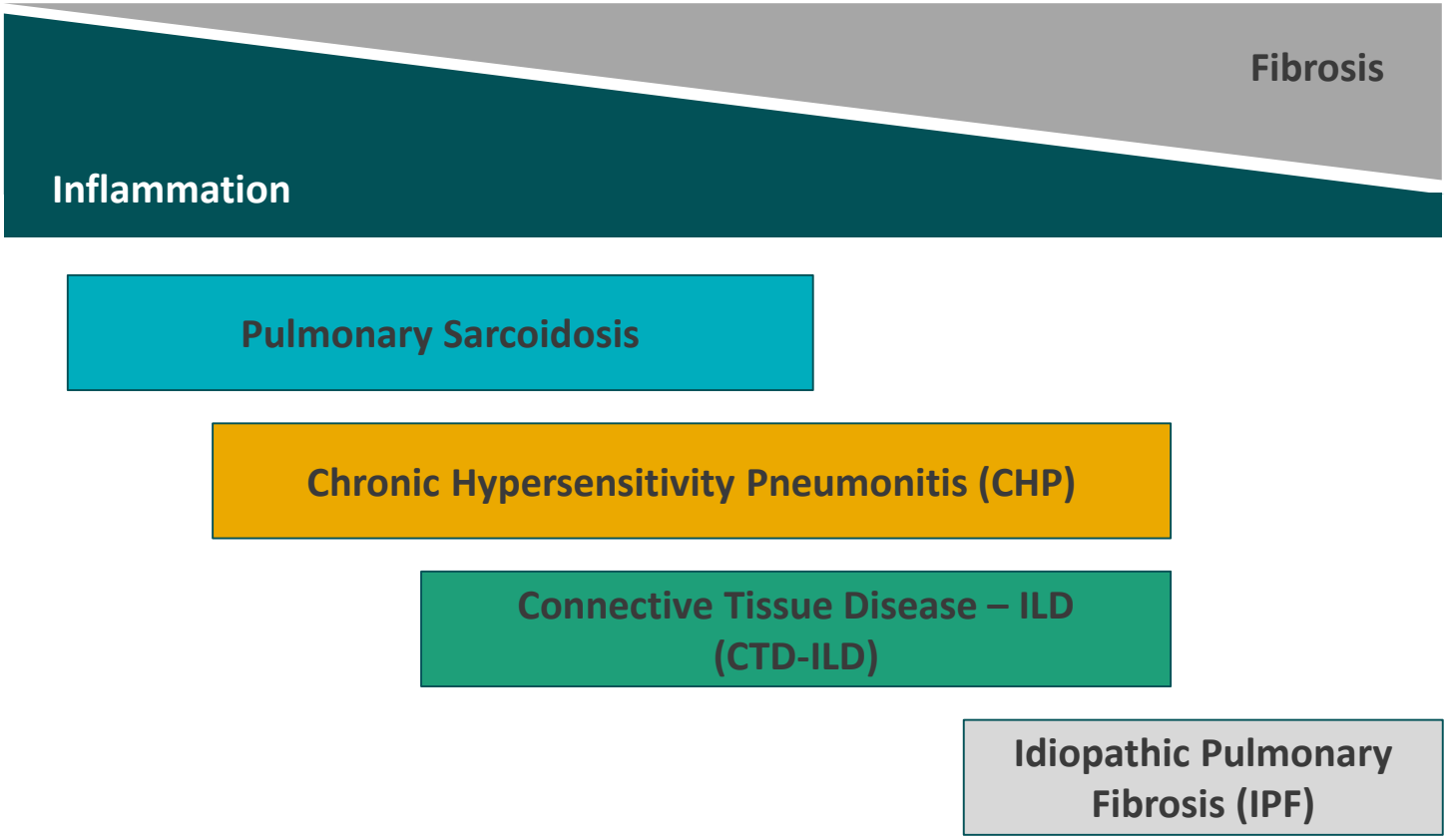
ILDs Share Persistent Immune Engagement



Slide adapted from Dr. Steven Nathan, Medical Director, Advanced Lung Disease and Transplant Program at Inova Fairfax Hospital, Falls Church, VA

High Unmet Need Persists

Pulmonary Sarcoidosis

- Systemic inflammatory disorder characterized by non-caseating granulomas (CD4+ T cell driven)
- US prevalence: ~200k
- ~30% of patients have chronic progressive disease, unresponsive to steroid treatment
- Current SOC: steroids - cytotoxic agents - TNF inhibitors (as disease progresses)

Chronic Hypersensitivity Pneumonitis (CHP)

- Exaggerated immune response to environmental antigen
- US prevalence: ~60k
- 5-year mortality: ~20%
- No effective therapeutic options

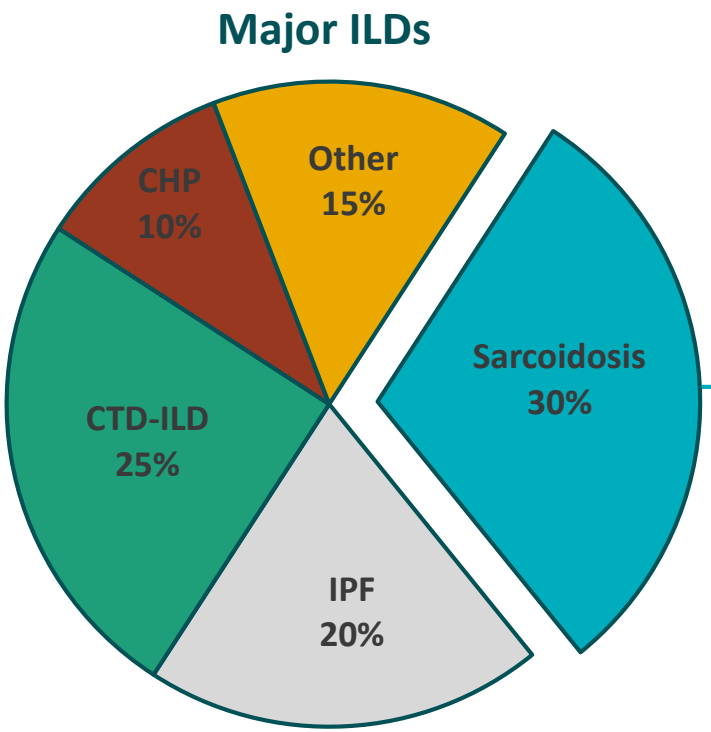
Connective Tissue Disease-ILD (CTD-ILD)

- Common manifestation in CTD: Clinically relevant ILD in 10% of Rheumatoid Arthritis and >50% of Scleroderma patients
- US prevalence: ~150k
- 5-year mortality: ~20%
- Current SOC: Mycophenolate mofetil or cyclophosphamide for Ssc-ILD; no SOC for RA-ILD

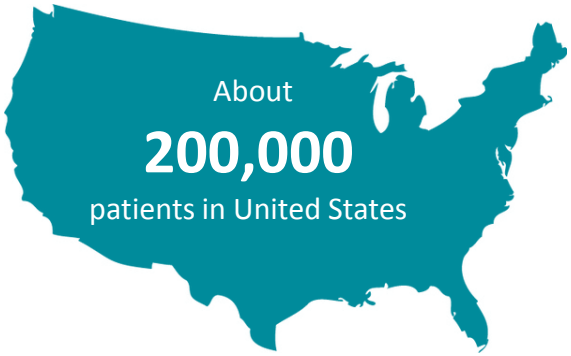
Idiopathic Pulmonary Fibrosis (IPF)

- Irreversible, progressive fibrotic disease of unknown cause
- US prevalence: ~135k
- 5-year mortality: 60-80%
- Current SOC: Nintedanib or pirfenidone (>$2b combined 2017 sales)

Sarcoidosis: A Major Form of ILD



$2-3b Global Opportunity(1)



50% require systemic therapy

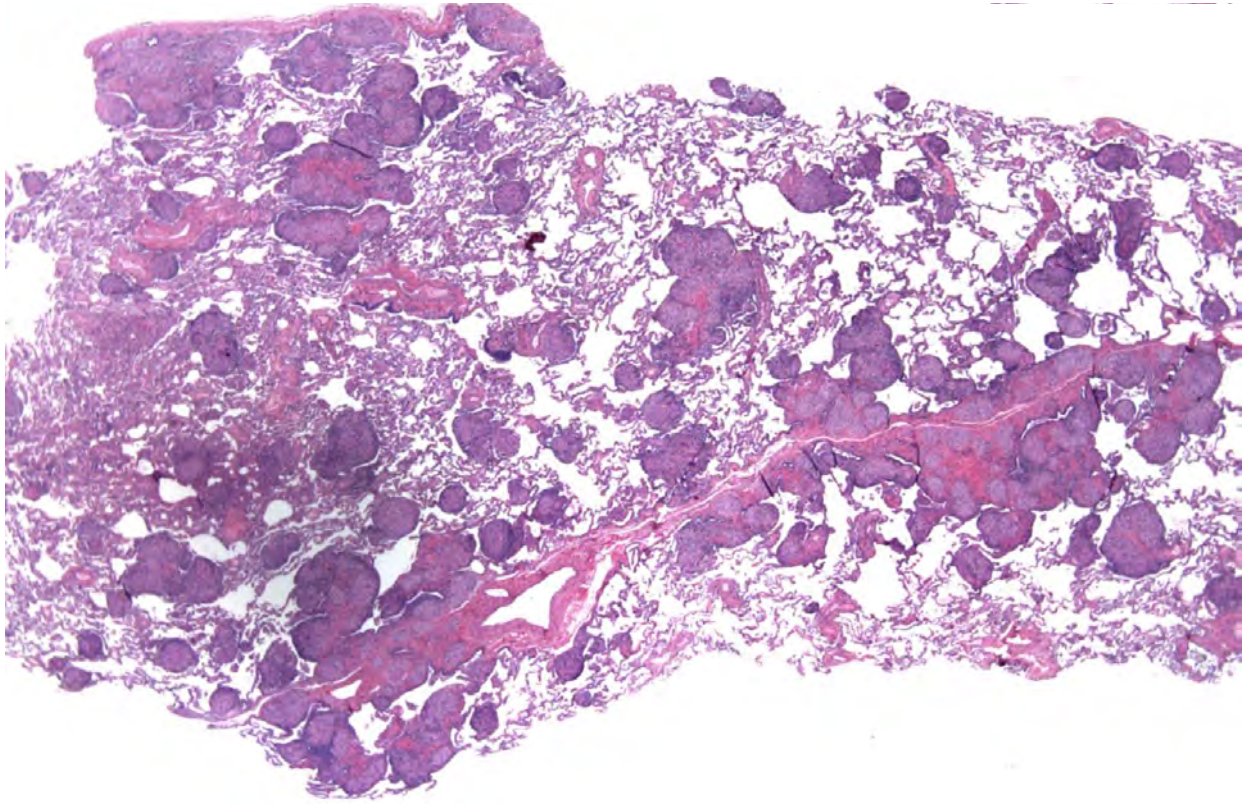
30% with chronic progressive disease despite currently available treatment

(1) aTyr estimates for inflammatory ILD: Pulmonary Sarcoidosis, CHP, CTD-ILD; excludes IPF

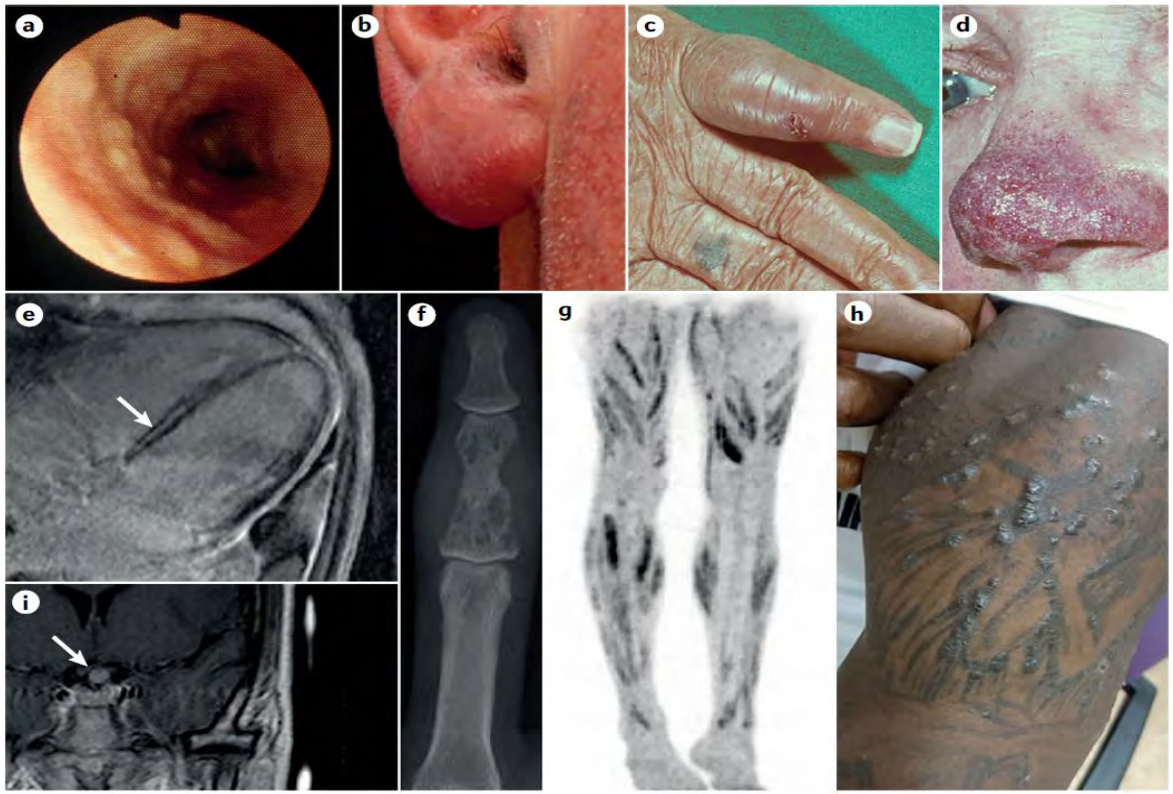
Sarcoidosis

Daniel A. Culver, DO
Cleveland Clinic

Sarcoidosis: a granulomatous disorder of unknown etiology

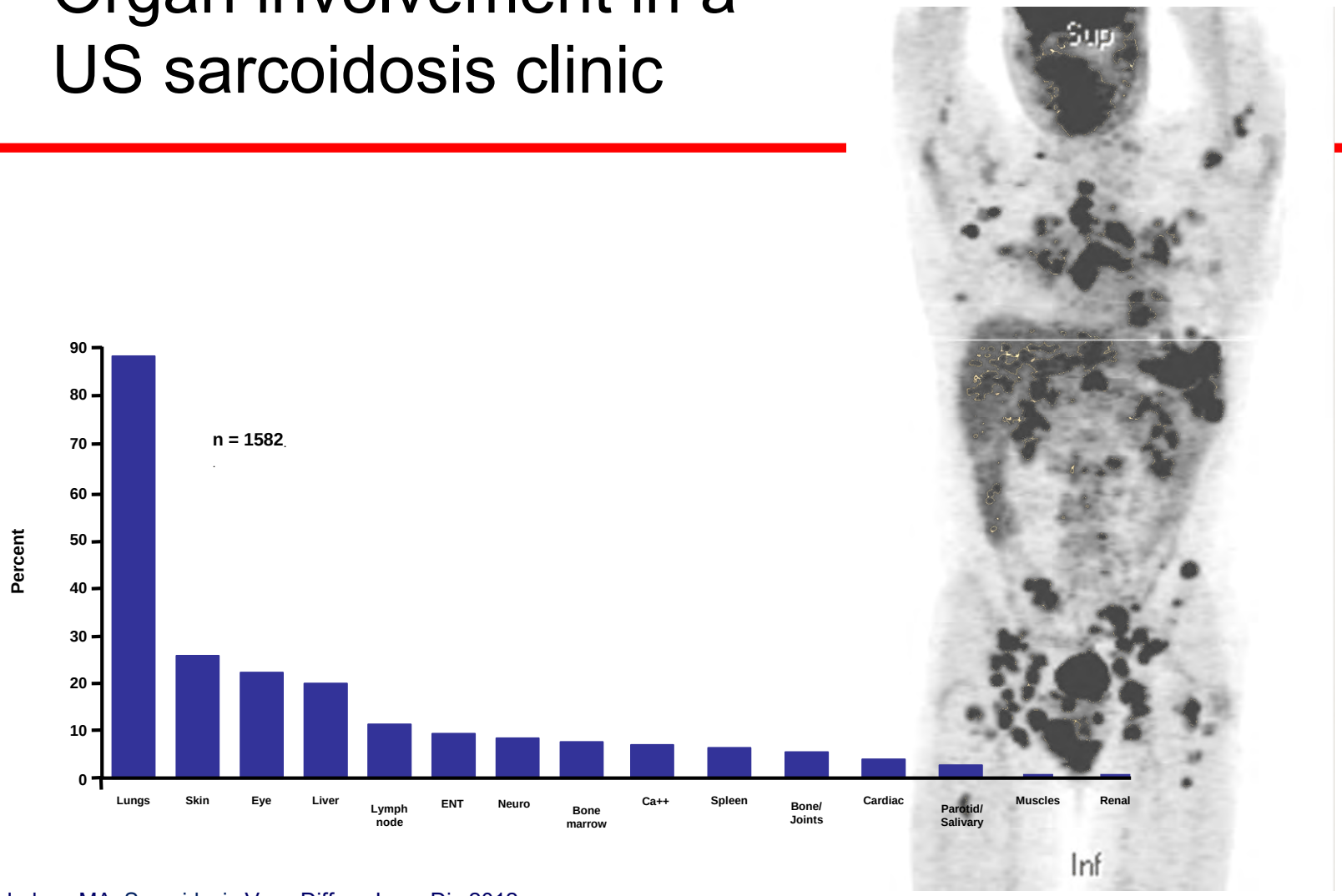


Sarcoidosis affects any organ



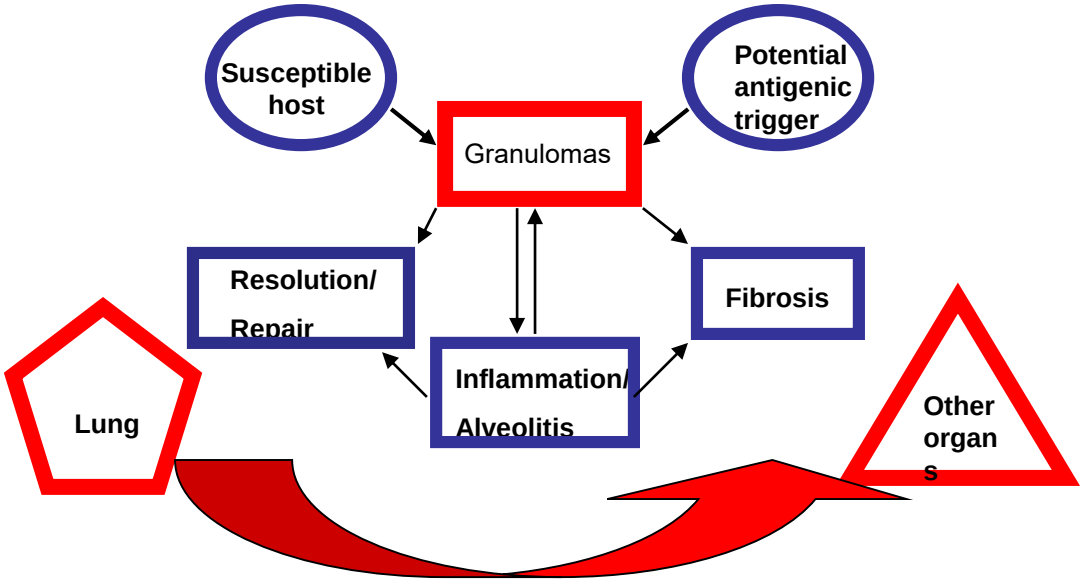
Grunewald J. Nat Rev Dis Primers

Organ involvement in a US sarcoidosis clinic



Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012

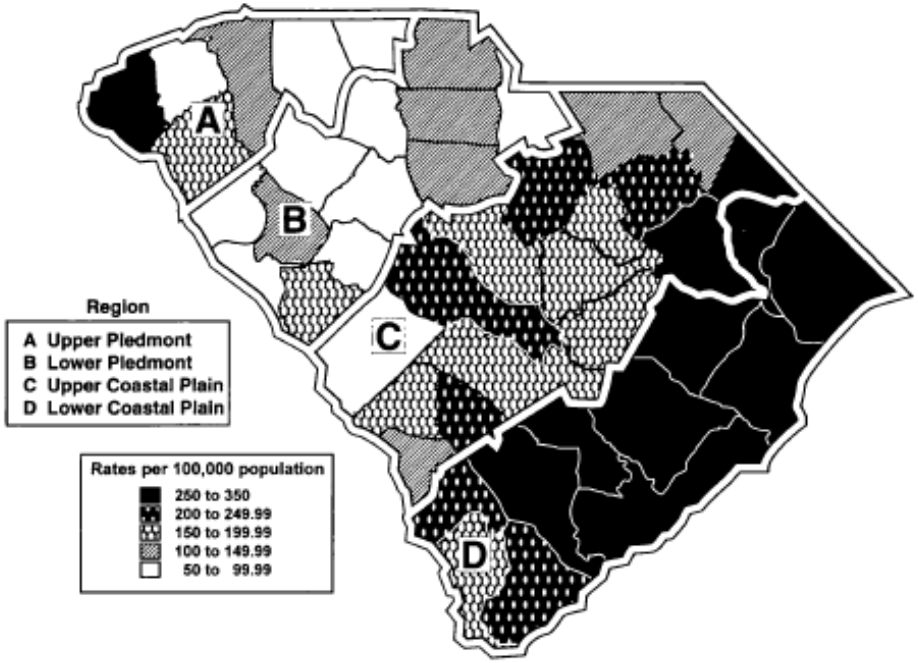
Pathogenesis and Natural History of Sarcoidosis: Current Paradigm and Key Issues



Key clinical features of sarcoidosis syndrome

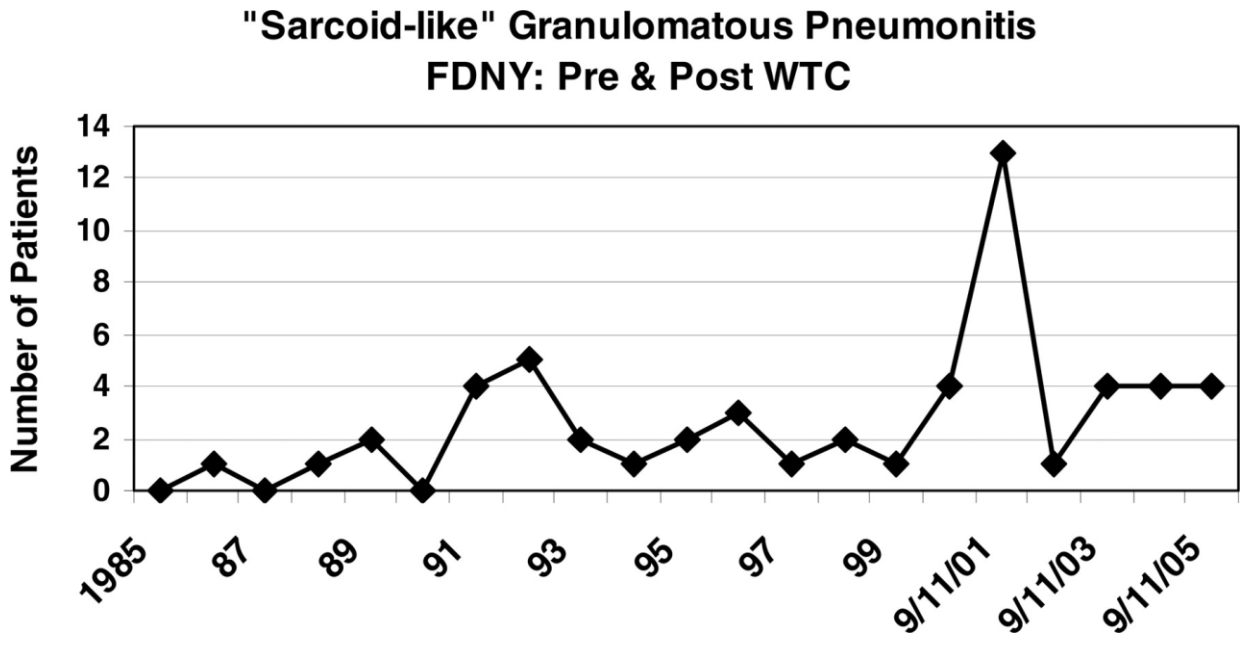
- *Sine qua non* is the granuloma
- Multisystem by definition
- Cases are concentrated in space and time
- Spontaneous remission is common
- Persistent disease does not always progress
- Racial and ethnic heterogeneity

Geographic variance: hospitalization for sarcoidosis



Kajdasz DK. Am J Epidemiol 1999

Sarcoidosis-like disease in fire-fighters



Izbicki G. Chest 2007

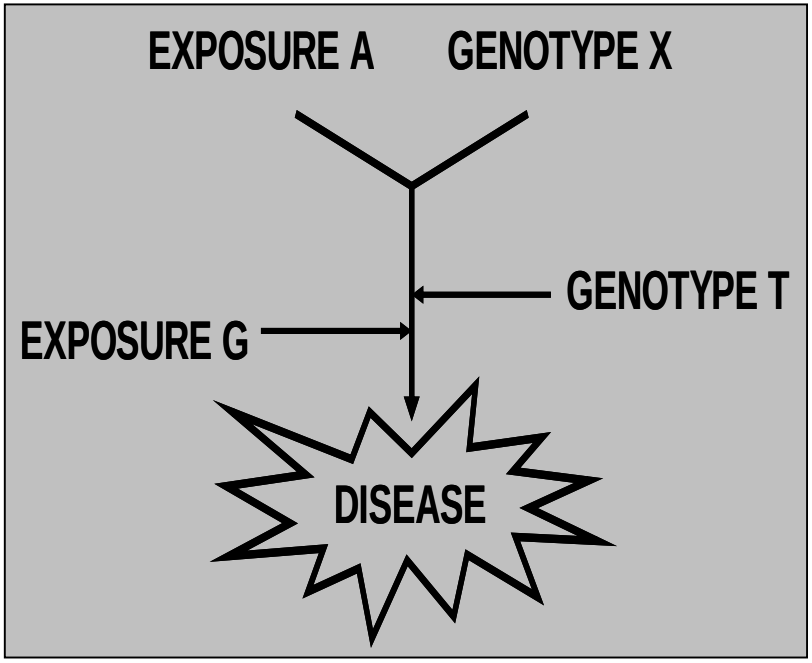
Photocopier use and risk of sarcoidosis

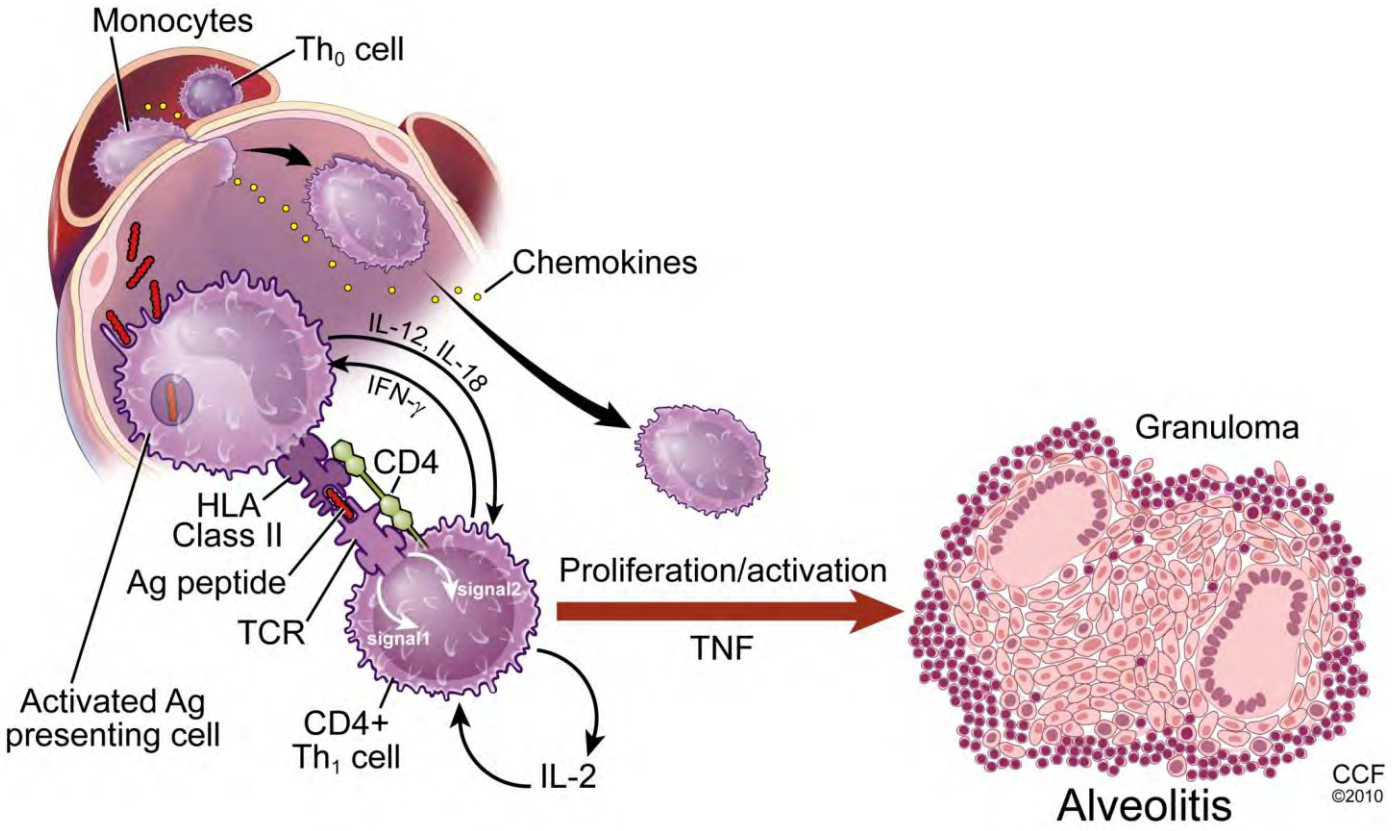
PHOTOCOPIER USE	TERTILE	ODDS RATIO[1] (95% CONFIDENCE INTERVAL)	P VALUE
Duration of use (years)	0	1	Reference
	1 – 7	1.37 (0.82, 2.31)	0.234
	> 7	2.01 (1.18, 3.42)	0.010
	Overall trend	–	0.012
Frequency of use (times per Week)	0	1	Reference
	1 – 3	1.10 (0.63 – 1.91)	0.746
	> 3	2.19 (1.31 – 3.65)	0.003
	Overall trend	–	0.003
Duration of use (min per episode)	0	1	Reference
	1 – 2	1.26 (0.72 – 2.20)	0.415
	> 2	1.83 (1.11, 3.02)	0.018
	Overall trend	–	0.018
Total lifetime exposure (hours)	0	1	Reference
	1 – 60	1.07 (0.61, 1.88)	0.824
	> 60	1.98 (1.18, 3.35)	0.010
	Overall trend	–	0.012

[1]adjusted for age, sex, method of data collection and history of clerical work

Rybicki BA. SVDLD 2004

Etiologic and modifier exposures and genes





Baughman RP, Culver DA, Judson MA. AM J Respir Crit Care Med 2011

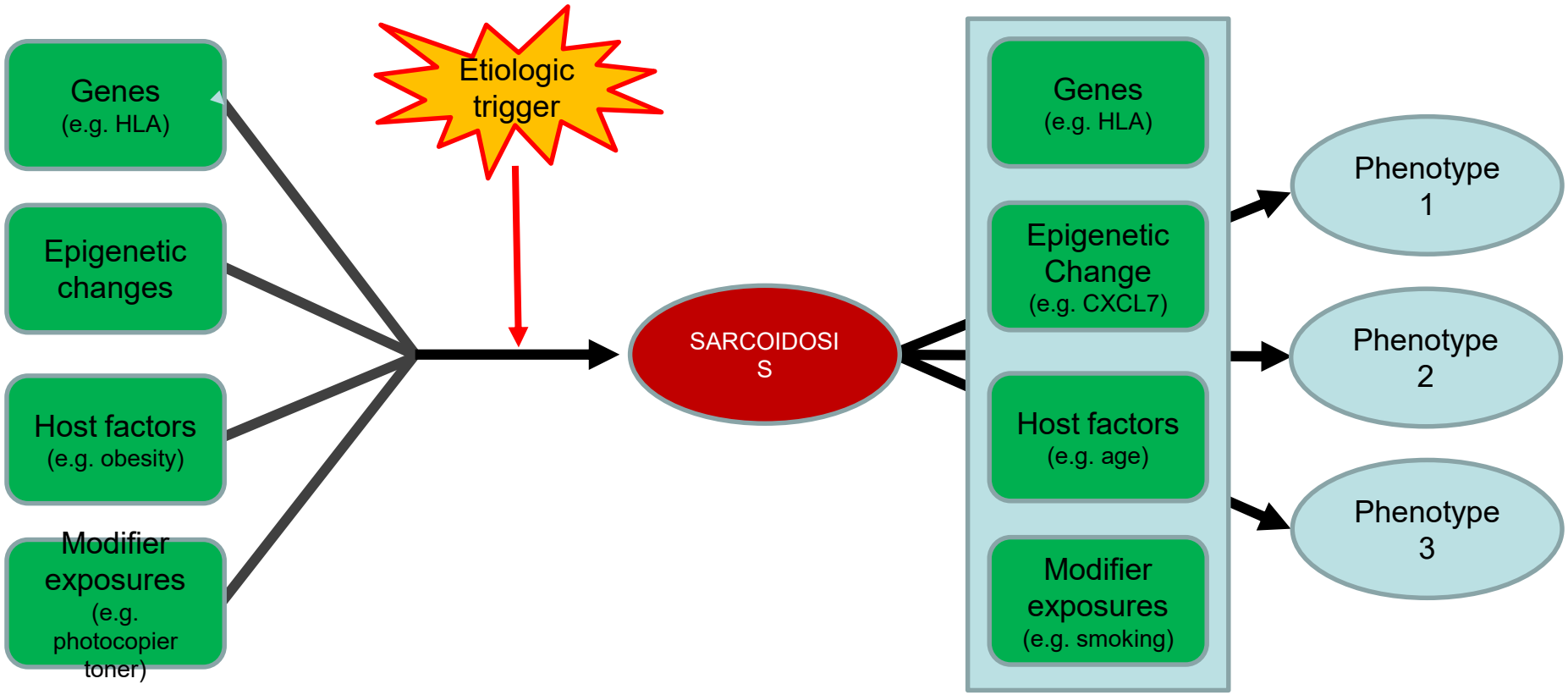
Some HLA associations

	Susceptibility	Phenotype
DRB1*03	+	Lofgrens' syndrome
DRB01*01	protective	
DRB15*01	protective	
DRB1*1101	+	
DRB1*0401	protective	↑uveitis
DQB1*0601		Cardiac (Japan)
DRB1*14	+	
DRB1*1201	+ (African-American)	
DRB1*0101	+ (African-American)	
DPB1*0101		Hypercalcemia
B*08	+	Resolving disease/arthritis

Rossman MD. Am J Hum Genet 2003
Sato H. Hum Mol Genet 2010

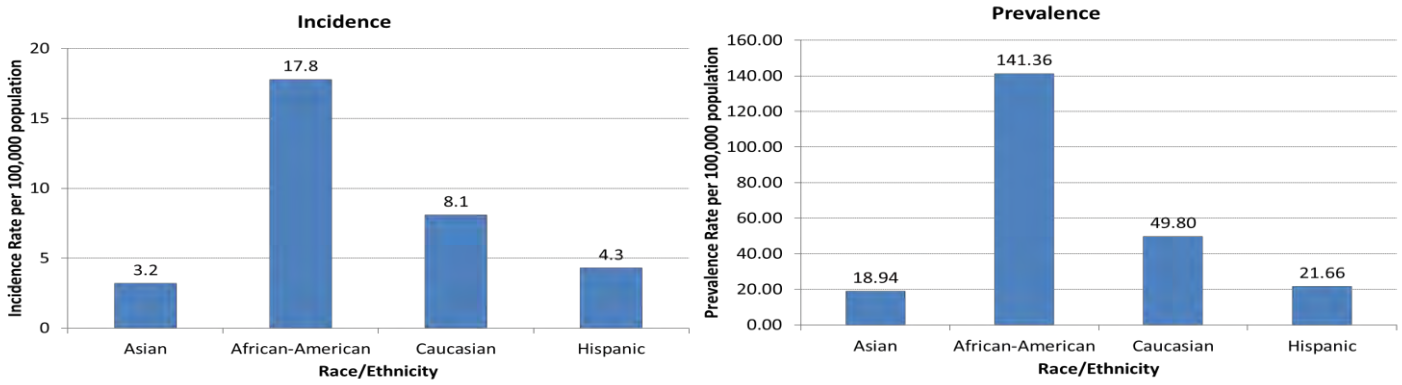
Levin AM. Am J Respir Cell Mol Biol 2014
Grunewald J. Am J Respir Crti Care Med 2004

Etiology is only part of the story



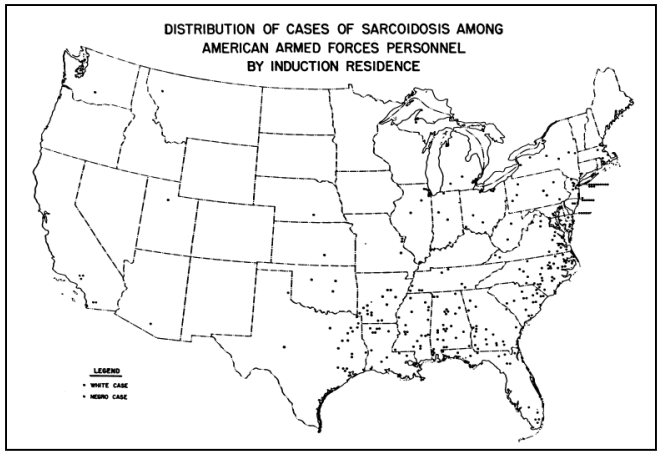
Sarcoidosis in the US

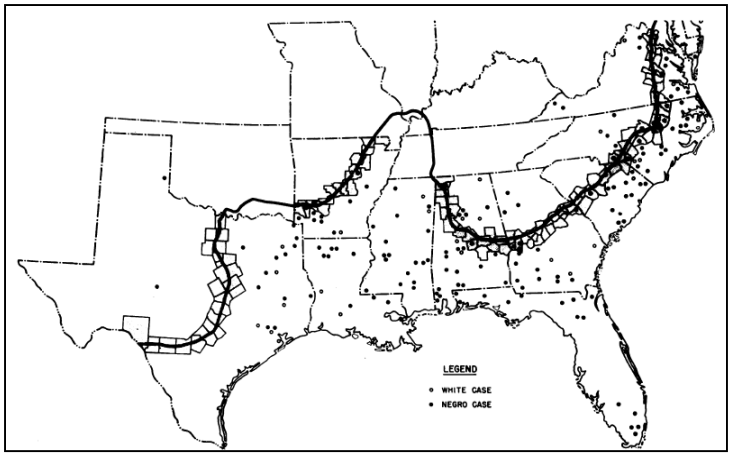
2010-2013 Optum Database



Baughman RP. Ann Am Thorac Soc 2016

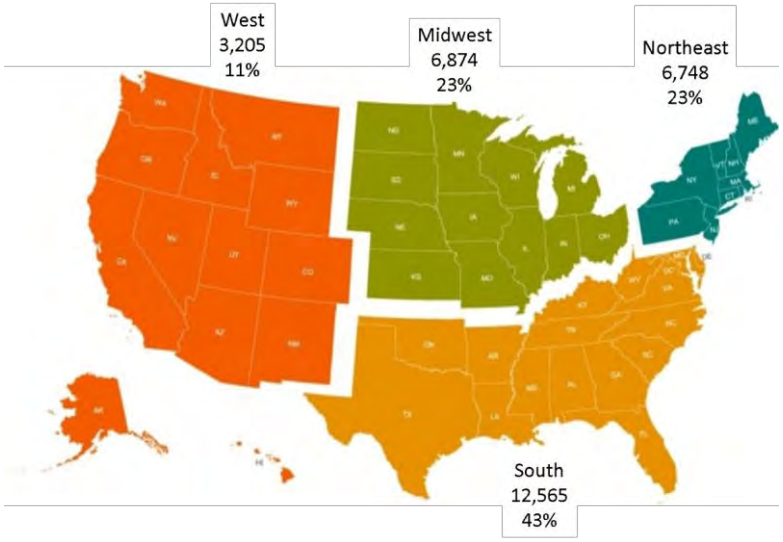
Sarcoidosis in US military personnel during WWII

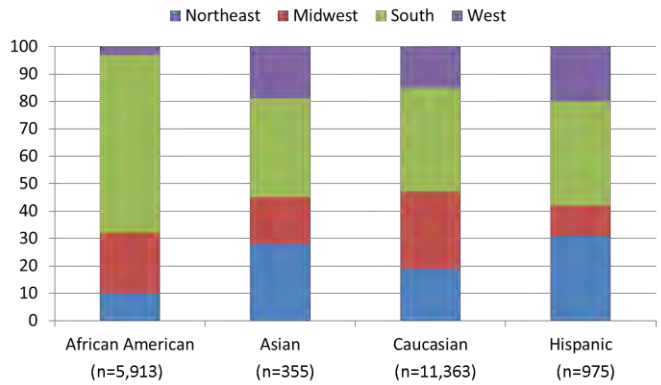




Gentry J Clin Invest 1955

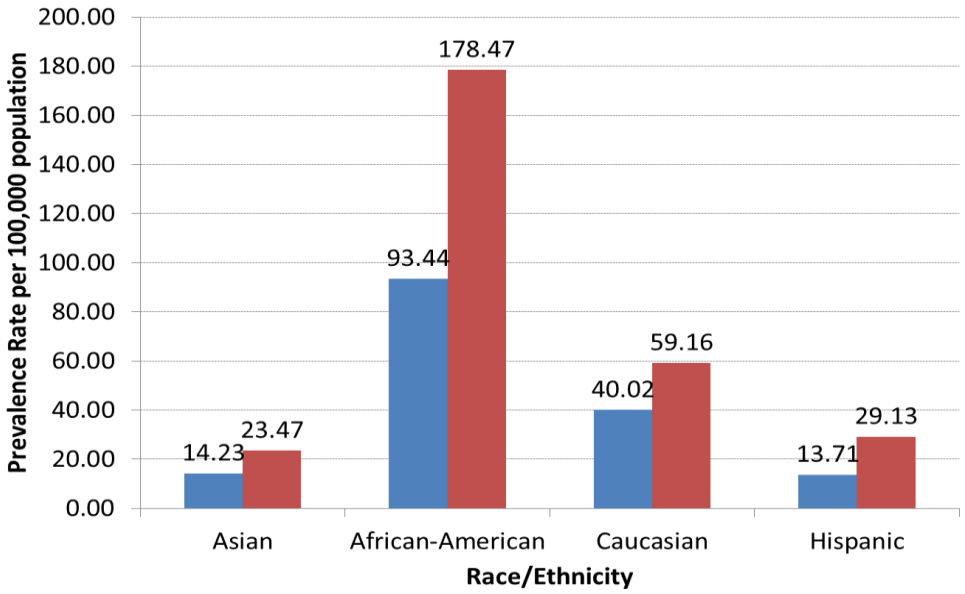
Sarcoidosis less common in the West





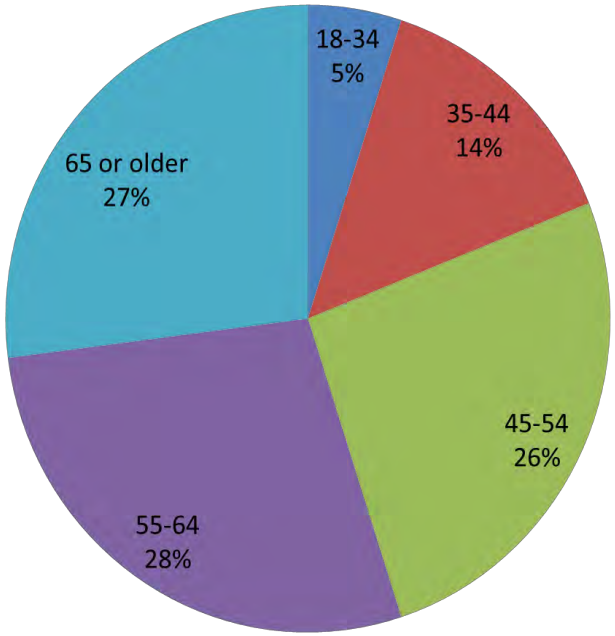
Baughman RP. Ann Am Thorac Soc 2016

Female predilection



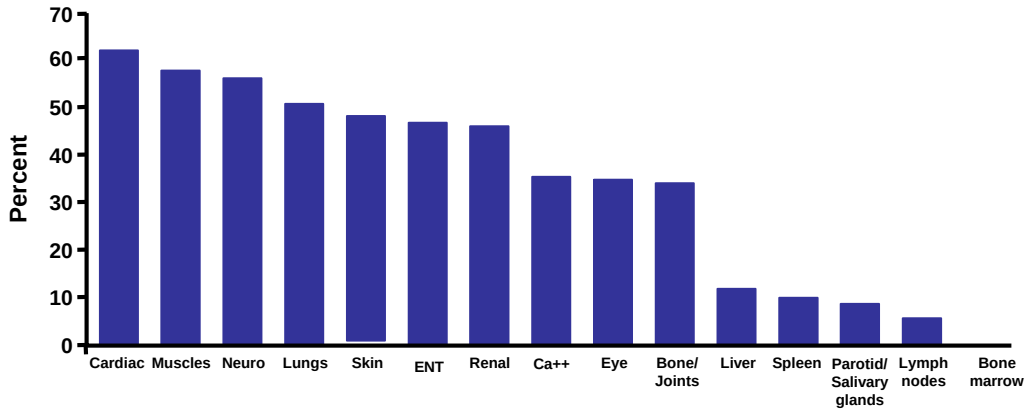
Baughman RP. Ann Am Thorac Soc 2016

Most patients are >55 at the time of diagnosis



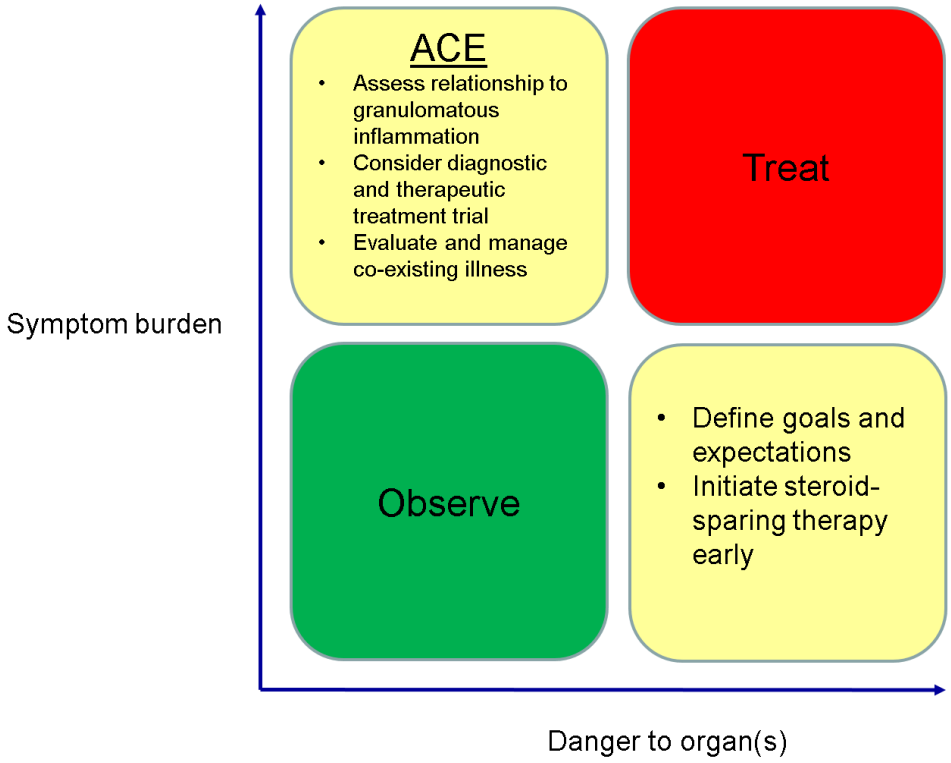
Baughman RP. Ann Am Thorac Soc 2016

Frequency of treatment requirement

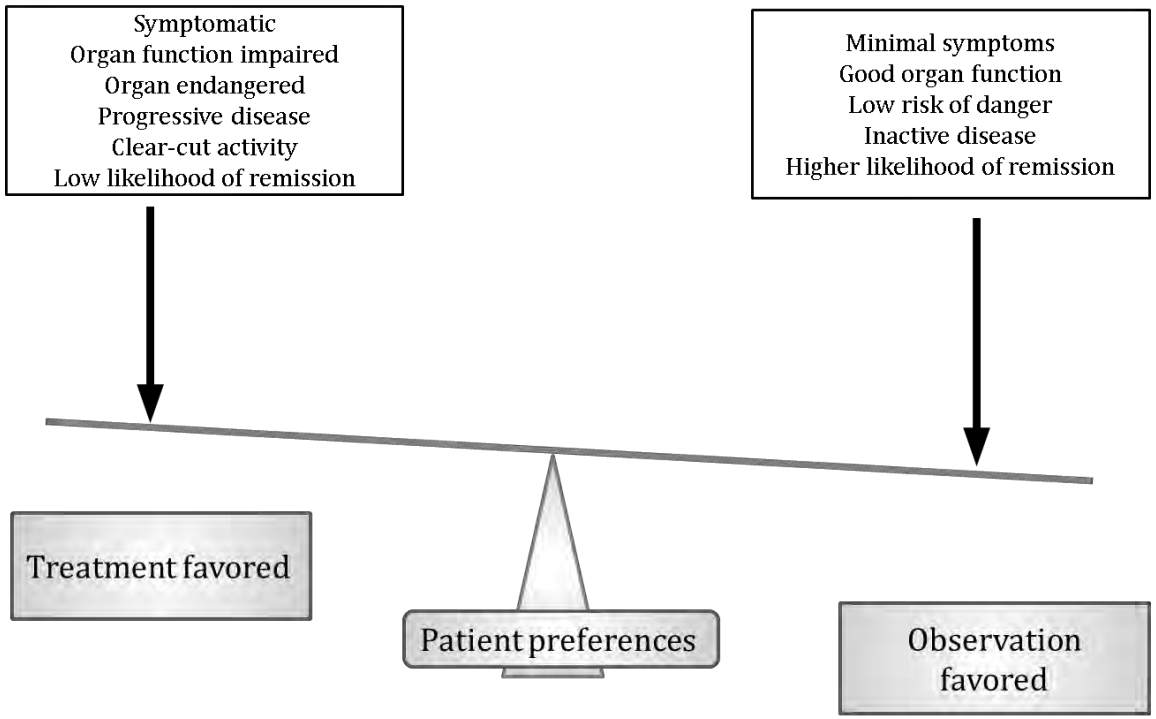


Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012

Treatment depends on symptoms and danger

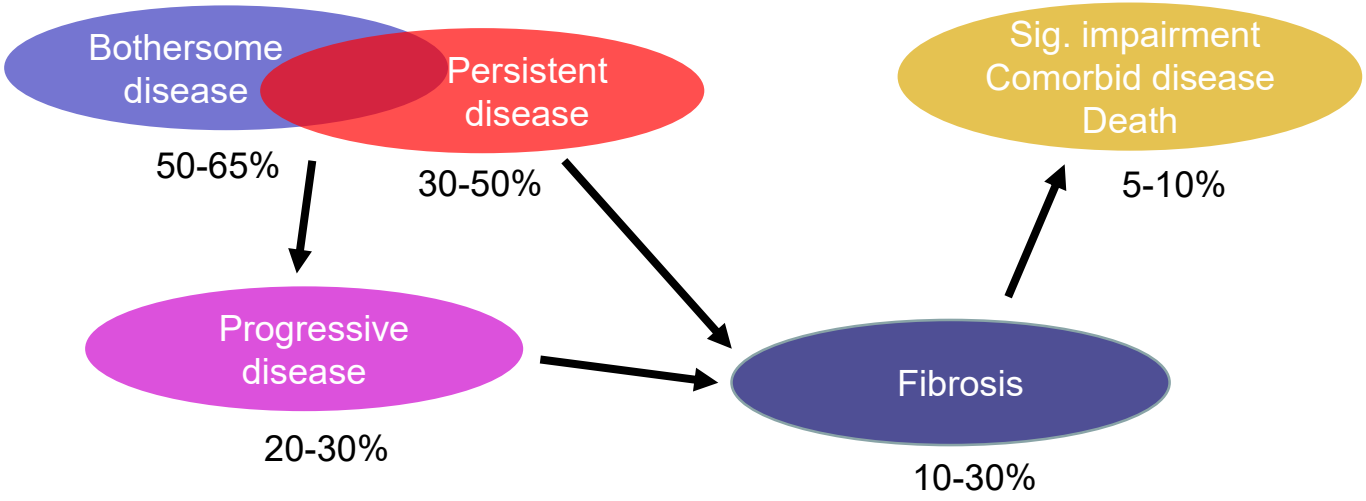


The decision to treat



Wijsenbeek MS. Clin Chest Med 2015

Which patient is at risk?



Baughman RP. QJM 2006; Mana J. Respiration 1994; Viskum K. Eur Respir J 1993; Nagai S. Curr Opin Pulm Med 1999; Judson MA. SVDLD 1993; Neville E. QJM 1983; Israel HL. Ann NY Acad Sci 1986

Prognostic markers

Increasing number of organs versus outcome†

Outcome at 2-5 yrs	1 organ (n=44)	2-3 organs (n=198)	4+ organs (n=53)
No important issue	64%	46%	13%
Significant organ function impairment	30%	43%	64%
Required assistance	7%	6%	23%

Neville E. QJM 1983; Lower EE. Arch Intern Med 1997; Sones M. Am J Med 1960;
Israel HL. Ann NY Acad Sci 1986; Schupp JC. Eur Resp J 2018; Takada K. J Clin Epidemiol 1993†

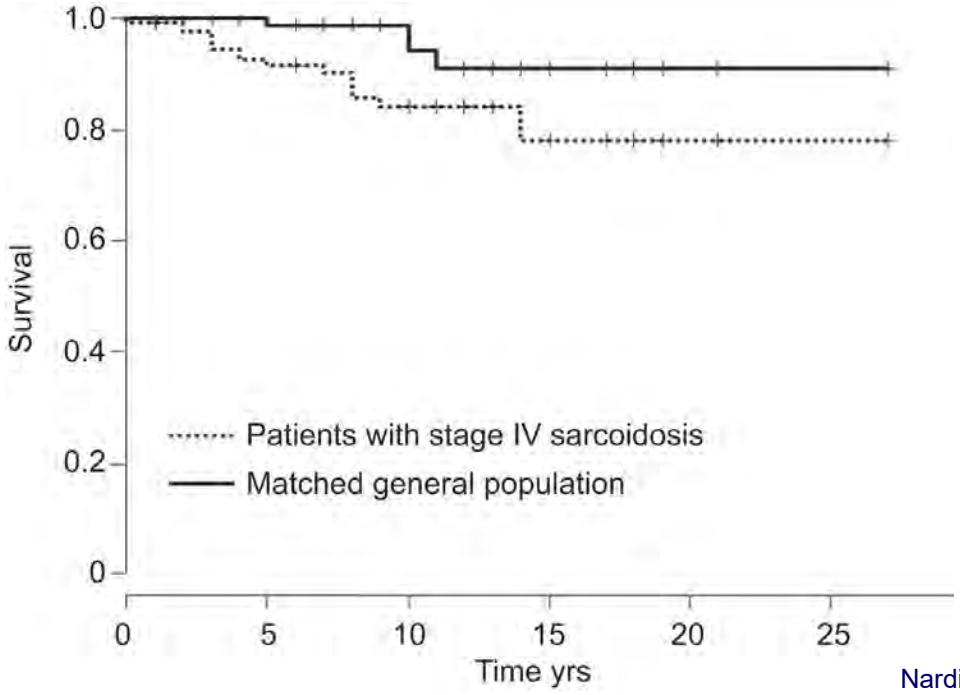
Risk Factors for Development of Advanced Disease Include Those of Persistent or Bothersome Sarcoidosis

Persistent disease	Clinically bothersome disease
Black race	Black race
Older age	More dyspnea at time of diagnosis
Female gender	Need for Tx 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	

Patel DC. Pulmonary Sarcoidosis: A Guide for the Practicing Physician 2014

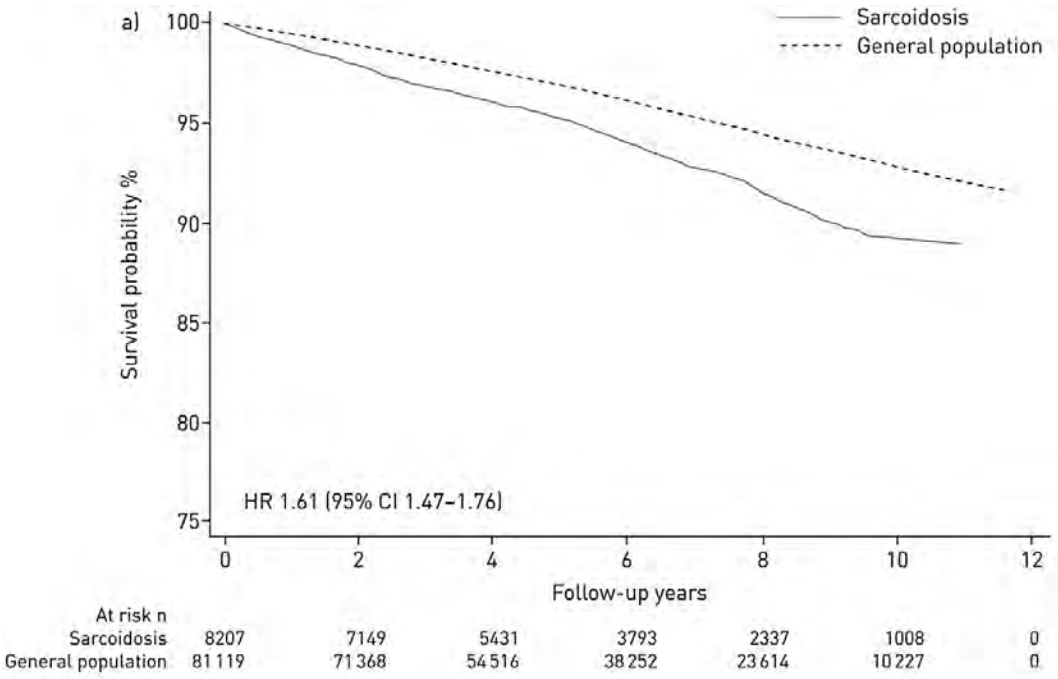
Fibrotic sarcoidosis impact on survival

Comparison of survival between patients with radiographic stage IV disease and a matched French general population (n=142).



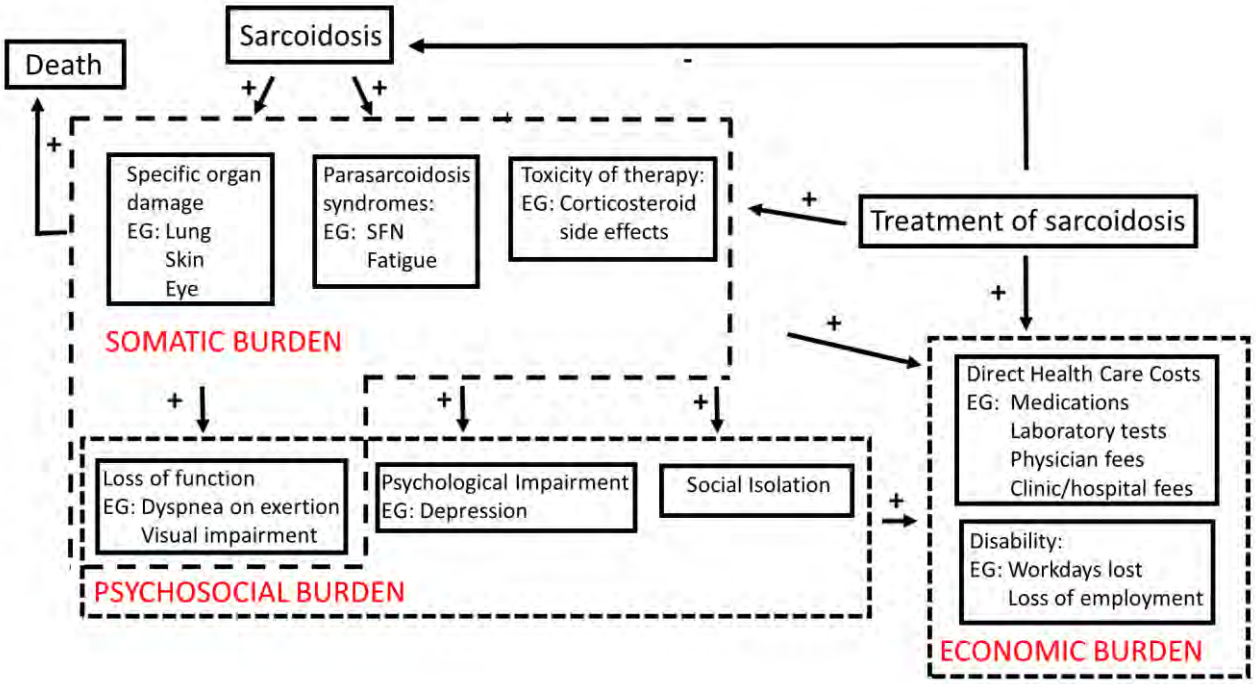
Nardi A. Eur Respir J 2011

Mortality in Swedish sarcoidosis patients vs general population



Rossides M. Eur Respir J 2018

Sarcoidosis burden



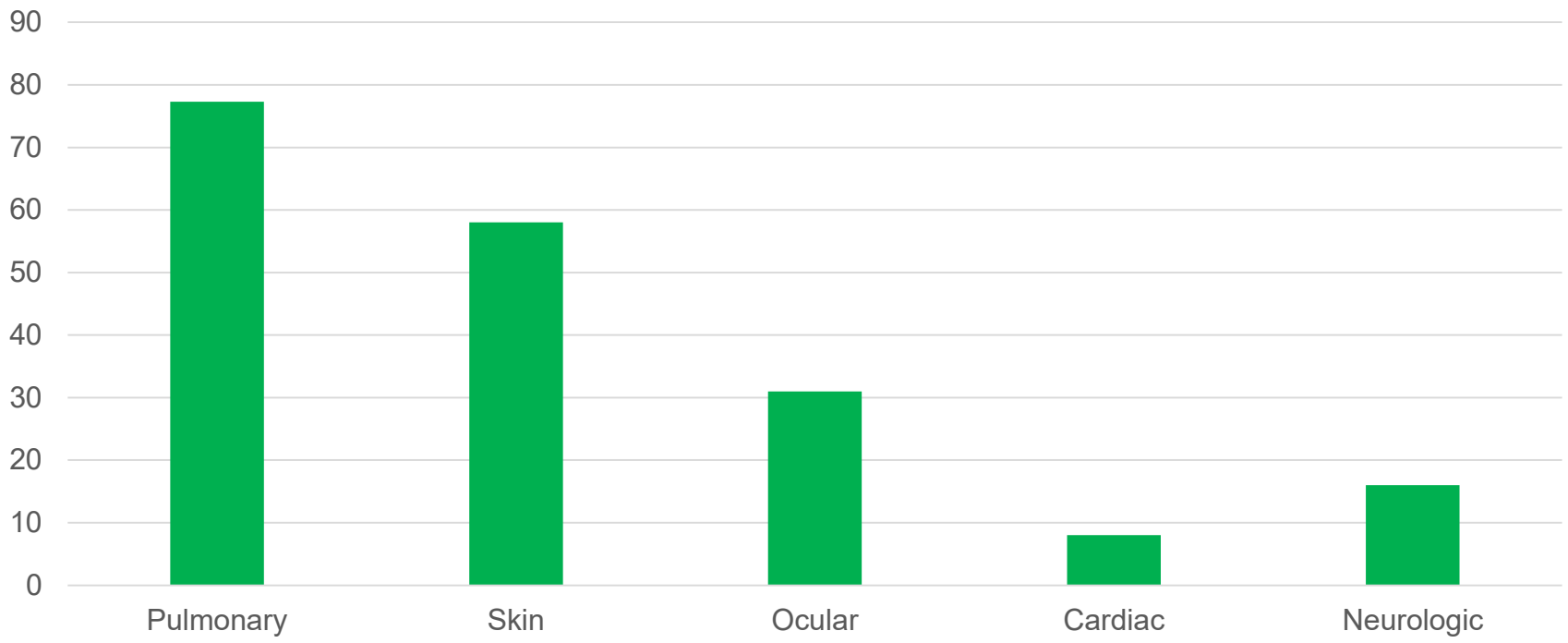
Gerke AK. Ann Am Thorac Soc 2017

FSR Sarcoidosis Registry

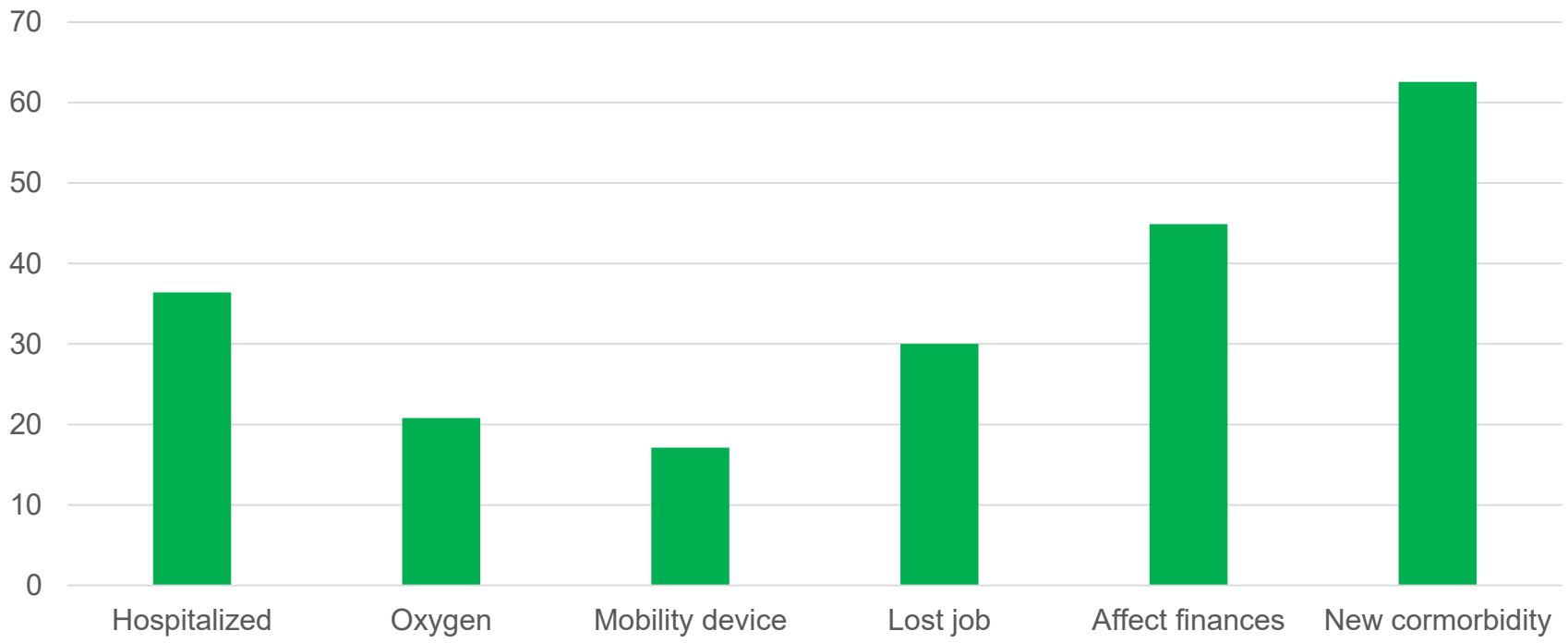
- Web-based, opt-in, longitudinal registry
- 2461 US-based respondents
- Outcome categories
  - Health outcomes
  - Social outcomes
  - Quality of life

Demographics	N (%)
Mean age (SD)	53.9 (10.9)
Female	1823 (74.1)
Race White Black Other Missing	 1798 (73.1) 435 (17.7) 218 (8.9) 10 (0.4)
Mean disease duration, yr	12.8 (11.9)
Anti-sarcoidosis medication Current Past None	 1559 (63.3) 512 (20.8) 341 (13.9)
Household income >$85,000 $35,000-84,999 <$35,000	 721 (29.3) 849 (34.5) 618 (25.1)
Insurance Private Medicare/Medicaid/other Government None	 1600 (65) 714 (29) 73 (3)

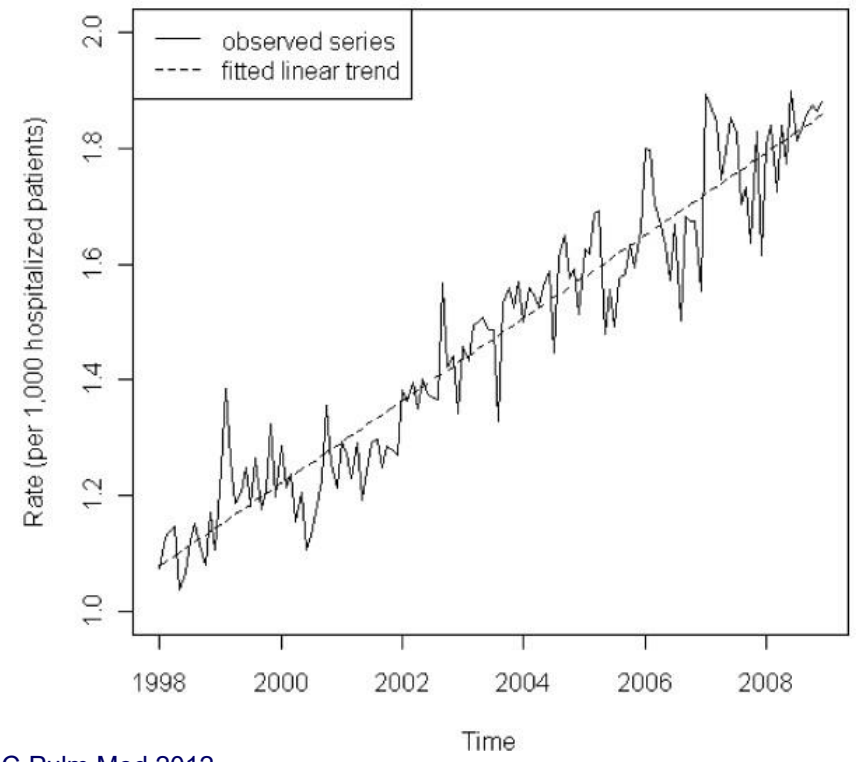
Main organ involvement



Outcomes


70
60
50
40
30
20
10
0
Hospitalized
Oxygen
Mobility device
Lost job
Affect finances
New cormorbidity

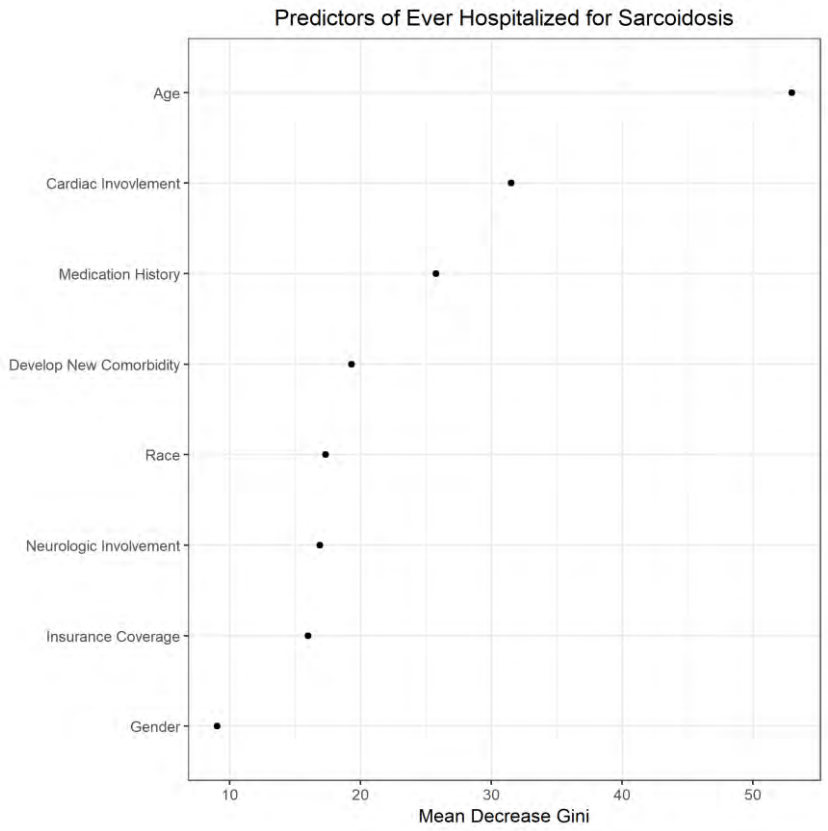
Hospitalizations are rising



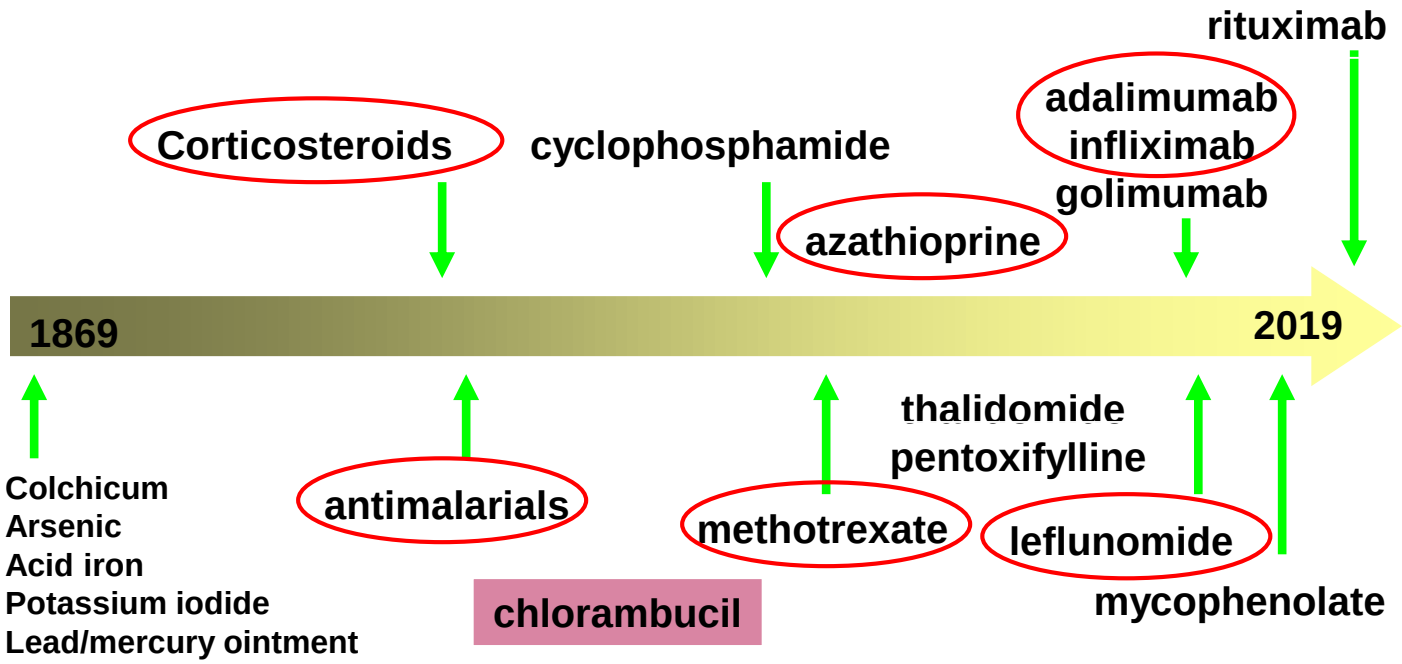
Gerke AK. BMC Pulm Med 2012

Ever hospitalized for sarcoidosis?

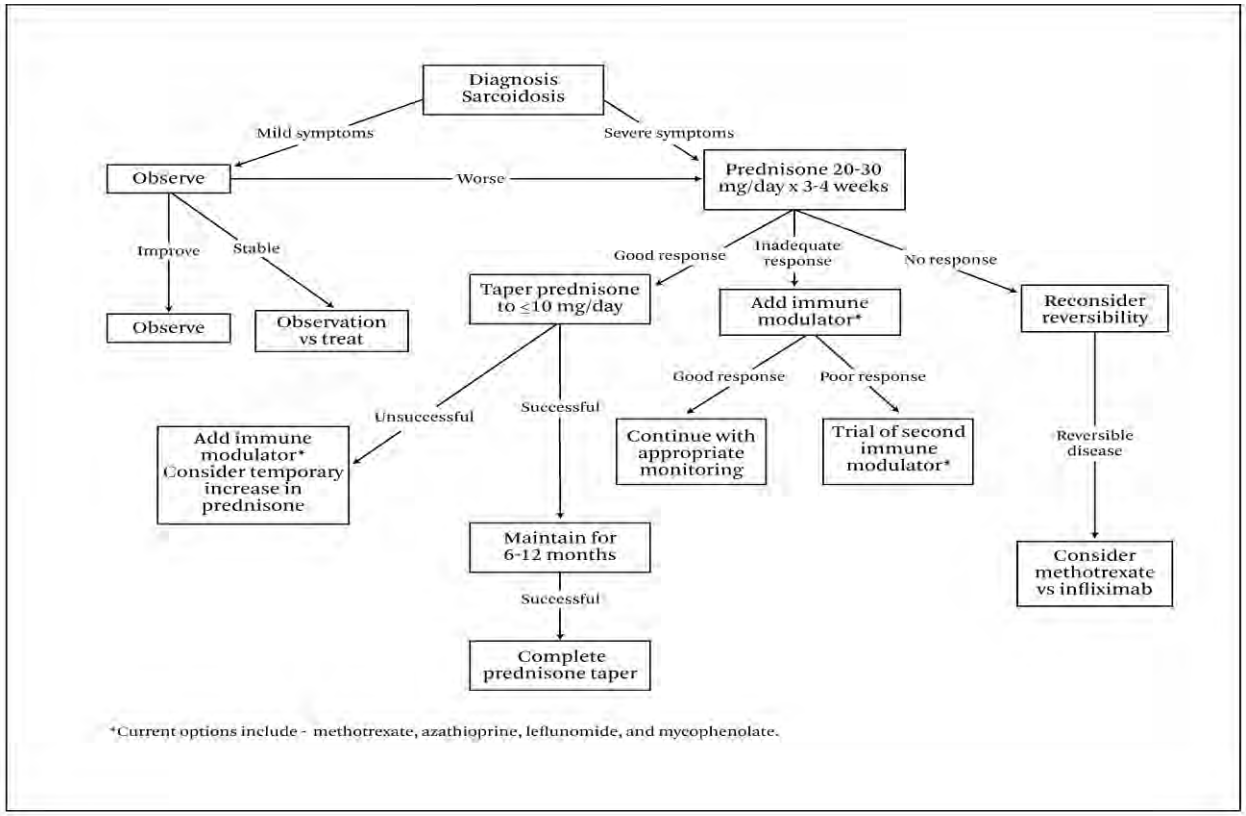
Variable	Odds ratio
Age/yr	0.99 (0.98-0.99)
Male gender	1.4 (1.1-1.9)
Race White Black Other	 Ref 1.7 (1.1-2.3) 1.0 (0.6-1.5)
Insurance Private Government None	 Ref 1.6 (1.2-2.1) 2.1 (0.99-4.5)
Neurologic	2.1 (1.6-2.8)
Cardiac	4.9 (3.3-7.3)
Sarcoidosis medications Never Past Current	 Ref 1.7 (0.96-3.0 3.1 (1.9-5.0)
Comorbidity	2.1 (1.6-2.7)



Treatment: main immunosuppressive options



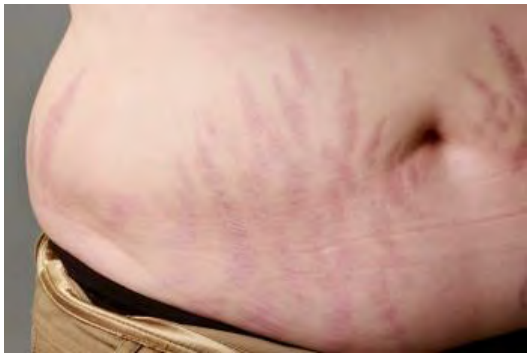
Treatment algorithm

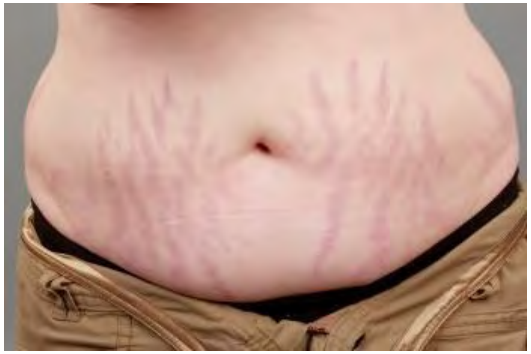


Lazar CA. SRCCM 2010

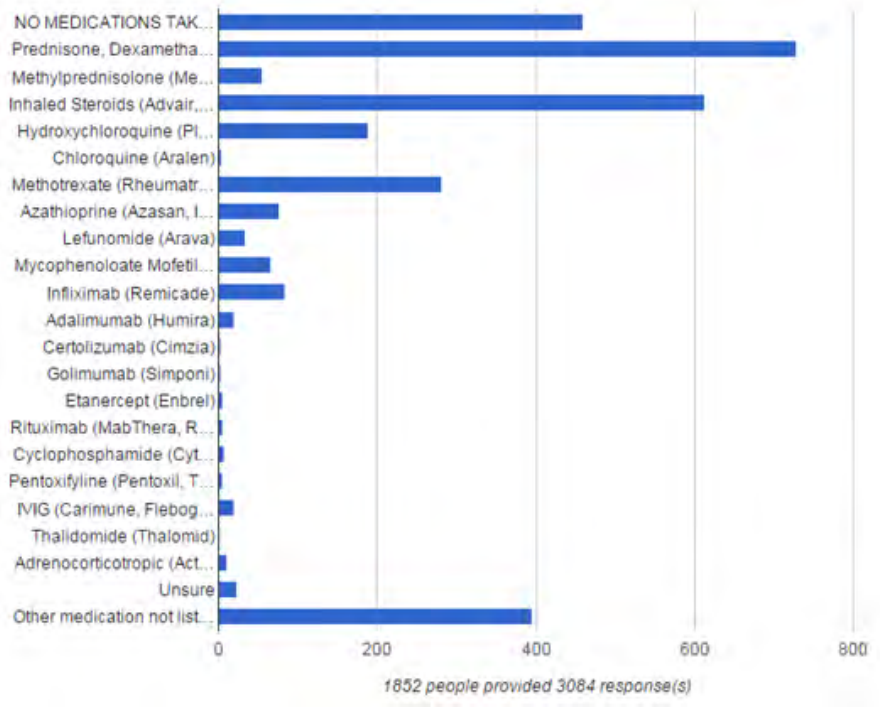
Glucocorticosteroids

- Glucocorticosteroids
  - first-line treatment in systemic sarcoidosis
  - most commonly used
- Alternative second-line agents important
  - steroid-resistance
  - steroid-induced side-effects
  - steroid-sparing





Medications in FSR registry population



Steroids are associated with impaired QOL

Table 3—*Differences in Predicted HRQL Scores Between Patient Groups Based on Oral Corticosteroid Treatment

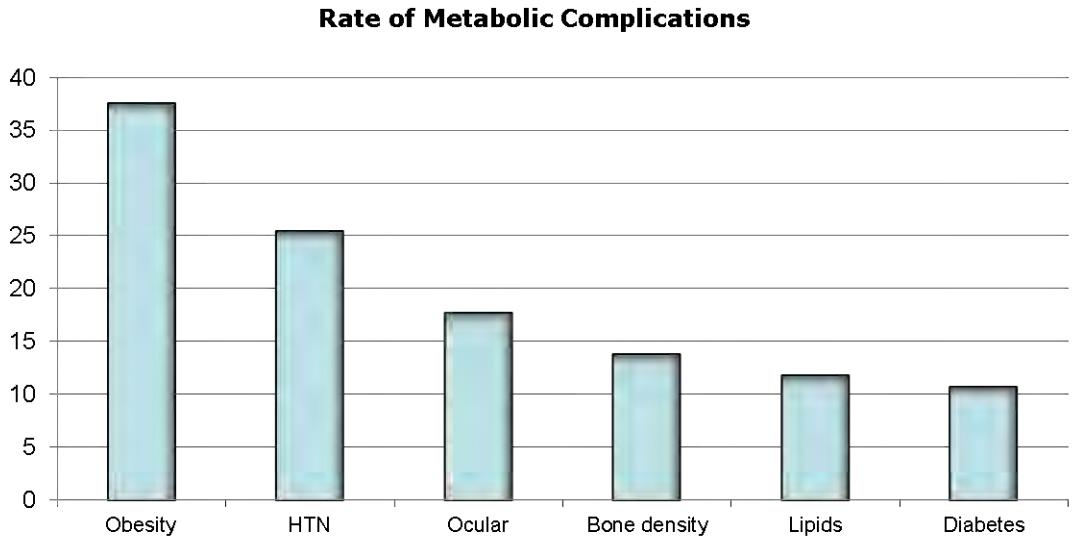
Group	Unadjusted Score	p Value	Adjusted Score†	p Value	Adjusted Score‡	p Value
SGRQ total						
Steroid users (n = 56)	52 (45–58)	<0.0001	49 (43–56)§	0.031	48 (44–53)‖	0.011
No steroids (n = 55)	37 (31–43)		39 (33–44)		39 (35–44)	
SF36-PCS						
Steroid users (n = 56)	31 (28–34)	0.011	32 (29–35)¶	0.048	32 (29–35)#	0.044
No steroids (n = 55)	37 (34–40)		37 (34–40)		37 (34–40)	
SF36-MCS						
Steroid users (n = 56)	42 (39–46)	0.055				
No steroids (n = 55)	47 (44–50)					

Cox CE. Chest 2004

Metabolic Complications among 154 new sarcoidosis patients seen at CCF

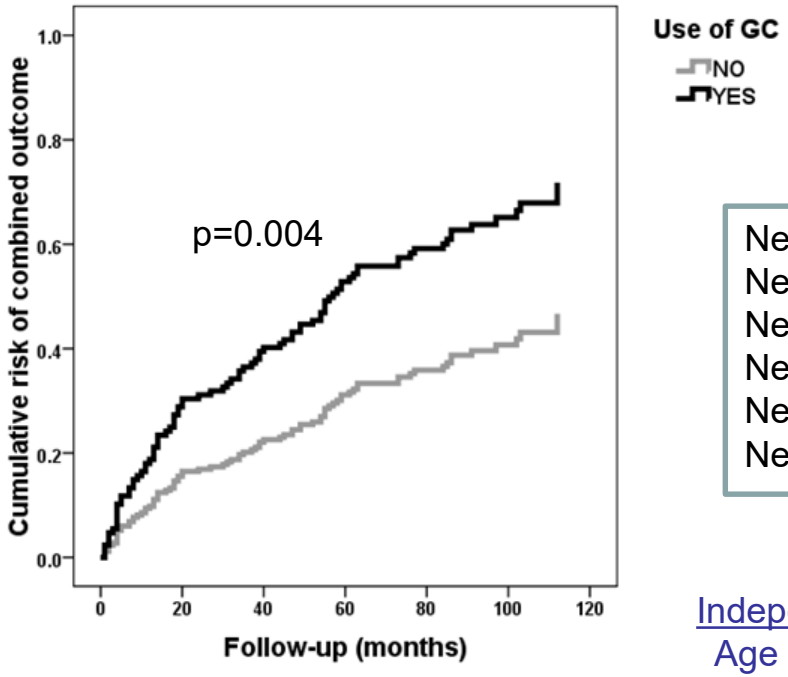
76 patients developed or had worsening

average of 1.9 ± 1 conditions per patient



Khan N. Resp Med 2017

Risk of steroid complications in 154 sarcoidosis followed longitudinally

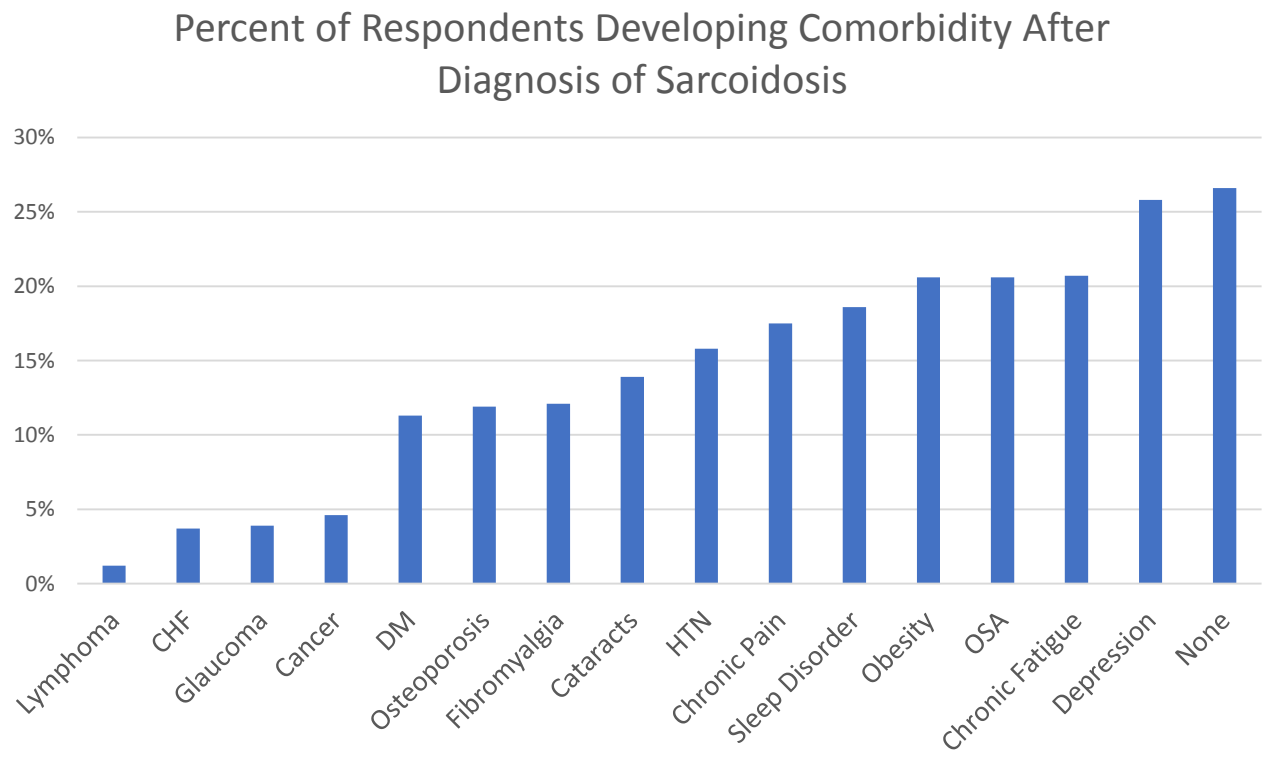


New obesity
New ocular complications
New bone density category
New or worsened HTN
New or worsened lipids
New or worsened diabetes

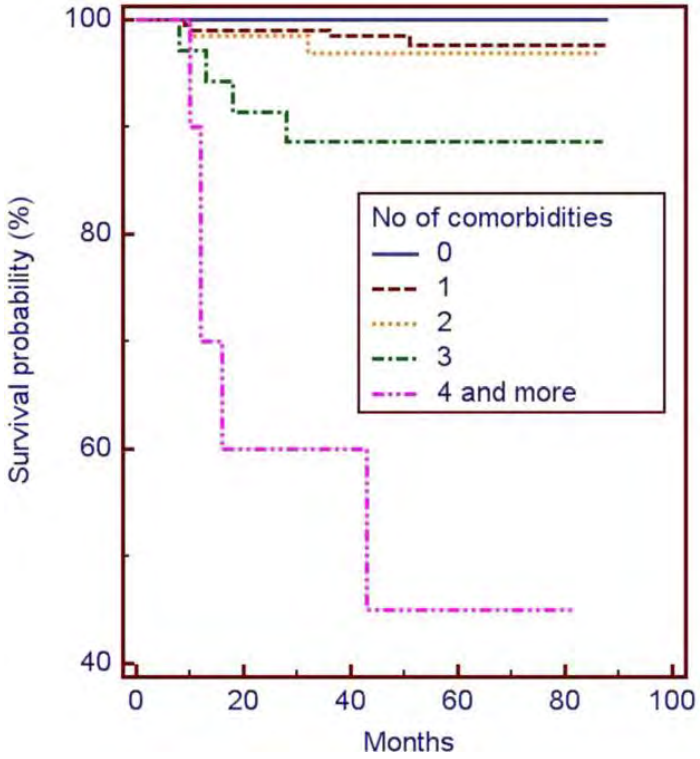
Independent predictors (HR)
Age per year: 1.02 (1.00-1.04)
Any GC: 1.91 (1.13-3.22)
Dose of GC (gram): 1.03 (1.1-1.6)

Khan NA. Respir Med 2017

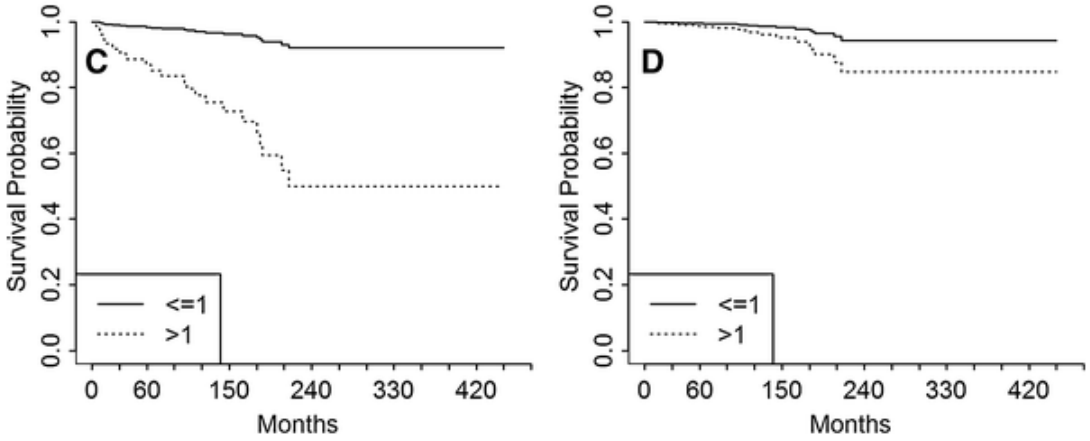
Self-reported comorbidities in registry patients



Presence of comorbidities effect on survival



Nowinski A. Clin Respir J 2018



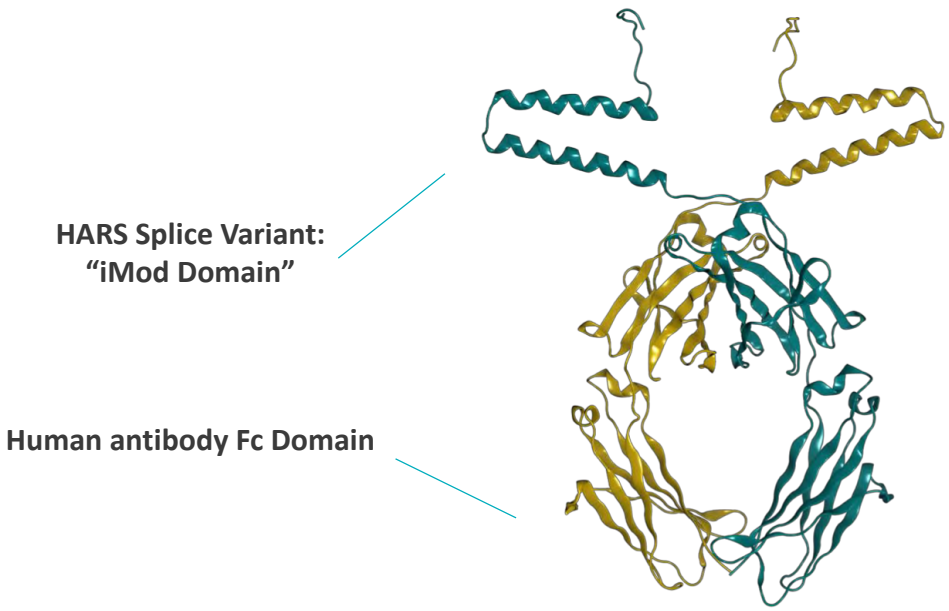
Brito-Zeron P. Lung 2018

Unmet needs

- Better understanding of the pathogenesis
  - Extant models just coming online will be helpful
- Prognostic stratification and targeted management
  - GRADS study, Gen-Phen study, and others will provide new insights
- Better therapies, with quicker onset of action and less toxicity

ATYR1923
Phase 1b/2a Study for Patients with Pulmonary Sarcoidosis

ATYR1923: Novel Engineered Protein Therapeutic



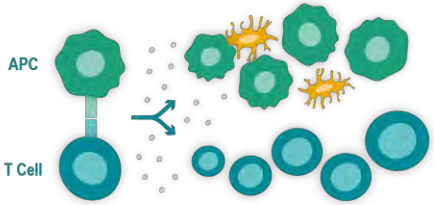
- iMod Domain of HARS enriched in the human lung
- Inhibits human T cell activation/cytokine release
- Binds selectively to Neuropilin-2 (NRP2)
- Regulates a number of immune cell-types, including: T cells, Neutrophils, Macrophages, Dendritic cells
- iMod Domain fused to Fc Domain to extend half-life
- Once-monthly IV dosing regimen

ATYR1923 Mechanism of Action in ILD

Disease Trigger

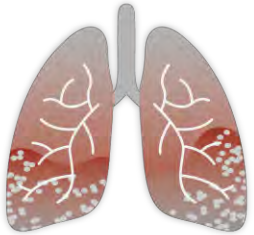
Organic; inorganic; infectious; autoimmune

Aberrant Immune Responses



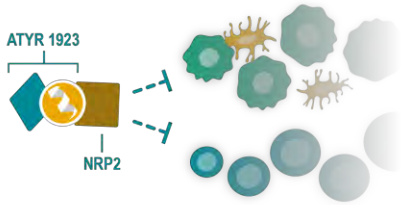
T-cell activation; Pro-inflammatory cytokine/chemokines triggering fibrotic pathways; NRP2 upregulation on immune cells

Lung Inflammation & Fibrosis



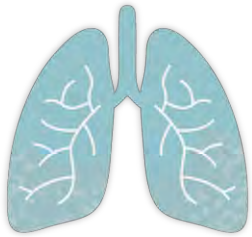
Persistent, unresolved inflammation in the lung can lead to fibrosis; patients experience chronic cough, dyspnea, mortality

ATRY1923 Dampens Immune Responses



ATYR1923 binds to NRP-2 and downregulates cytokine and chemokine production and T-cell activation

Stabilized Lung



Reduced inflammation and fibrotic deposition; symptom relief, stabilized lung function*

*aTyr hypothesis

aTyr

Pre-Clinical Translational Data Supports ILD Development

Bleomycin-Induced Lung Injury (IPF) – Mouse	• ATYR1923 reduced fibrosis and inflammation • Comparator: pirfenidone • Presented at ATS, May 2017
Bleomycin-Induced Lung Injury (IPF) – Rat	• ATYR1923 returned lung function to normal and reduced fibrosis and inflammation • Comparator: nintedanib • Presented at ATS, May 2018
Sclerodermatous chronic-graft vs host disease (SSc-ILD) – Mouse	• ATYR1923 reduced lung and skin fibrosis • Comparator: nintedanib • Presented at Scleroderma Foundation Patient Conference, July 2018
SSc-cGVHD (SSc-ILD); *P. acnes* (Sarcoidosis); *S. rectivirgula* (CHP); SKG (Ra-ILD) – Mouse	• ATYR1923 demonstrated stage-dependent anti-inflammatory and antifibrotic effect in various experimental models of ILD • Comparator: various • Presented at ATS, May 2019

PK Profile Supports Potential Once-Monthly Dosing

Phase 1 Healthy Volunteer Study Completed in Australia

- Positive data announced in June 2018
- Randomized, double-blind, placebo-controlled, single ascending dose (N=36 HVs)
- ATYR1923 was generally well-tolerated with no significant adverse events

Phase 1b/2a Study in Pulmonary Sarcoidosis

Objectives	• Evaluate safety, tolerability, PK, and immunogenicity of multiple ascending doses of ATYR1923 • Evaluate signals of drug activity through steroid dose reduction and FDG-PET/CT changes
Design	• Randomized, double-blind, placebo-controlled, multiple ascending dose
Population	• Histologically confirmed pulmonary sarcoidosis • Requiring ≥10 mg prednisone (steroid) treatment; capable of steroid taper • Symptomatic/active disease at baseline by ^{18F}-FDG-PET/CT, Pulmonary Function Tests
Dosing	• 3 sequential cohorts, 12 patients each • 2:1 randomization • ATYR1923 doses: 1.0, 3.0, and 5.0 mg/kg
Duration	• 24-week study period • Steroid taper phase down to 5 mg by week 8 • 16-week maintenance phase
Sites	• Up to ~15 leading pulmonary sarcoidosis centers • Collaboration with the Foundation for Sarcoidosis Research

Phase 1b/2a Study Endpoints

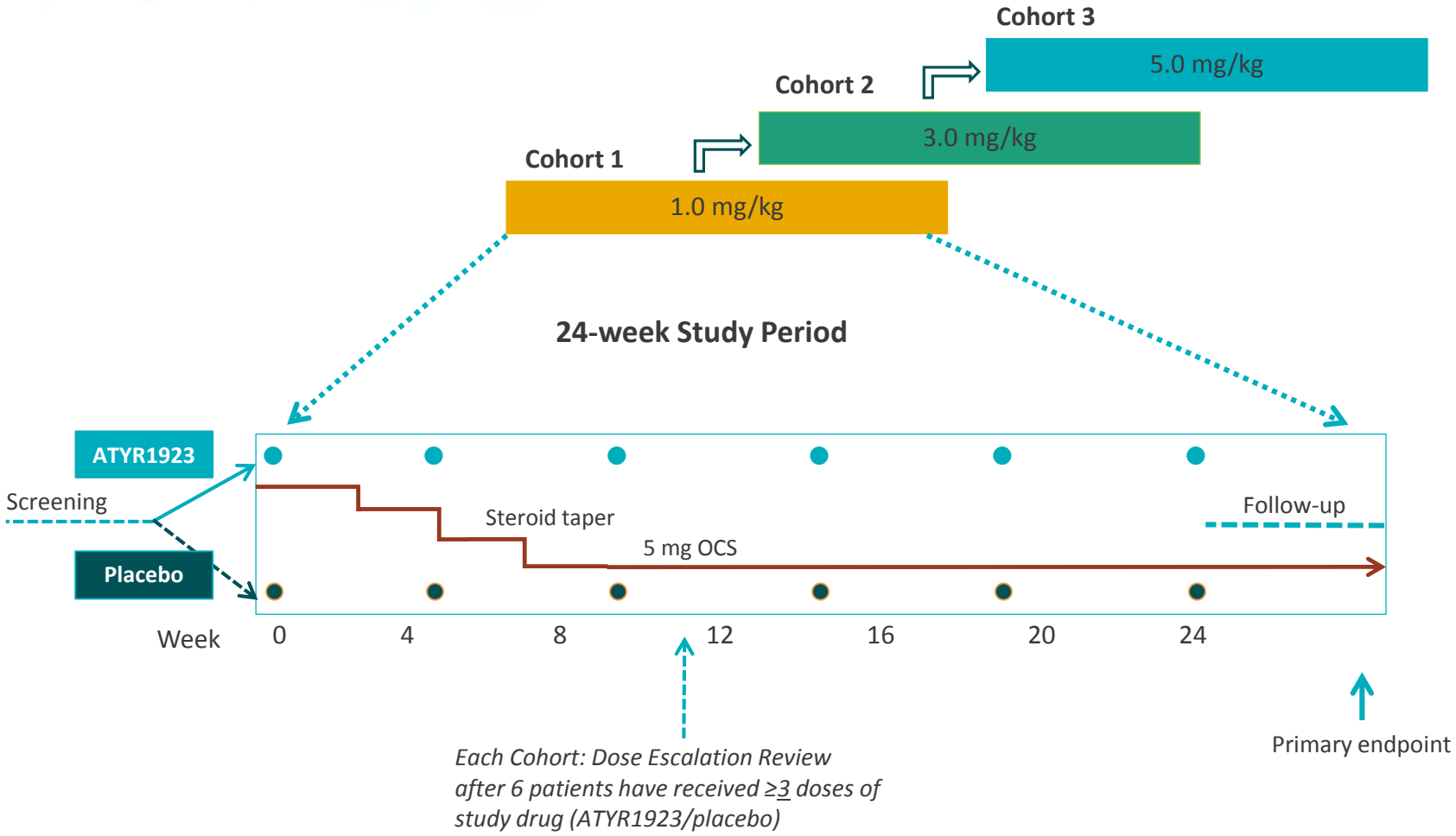
Primary

- Safety and tolerability of multiple ascending IV ATYR1923 doses

Secondary

- Steroid-sparing effect
- Immunogenicity
- Pharmacokinetics (PK)
- Exploratory efficacy measures: FDG-PET/CT imaging; Lung function (FVC); Serum biomarkers; Health-related quality of life scales

Phase 1b/2a Study Schema



Phase 1b/2a Study in Pulmonary Sarcoidosis Initiated

Status	• Up to ~15 leading Pulmonary Sarcoidosis centers • New site activation ongoing • Patient enrollment ongoing
Timelines	• Interim data: 4Q 2019 • Study completion: mid-2020(1)
Possible Future Development	• Registrational trial in Pulmonary Sarcoidosis • Initiate P2 studies in other types of interstitial lung disease (e.g. CTD-ILD; CHP)

(1) Dependent on patient enrollment

Accelerating Value Creation from New Biology

Platform of New Biology:

Discovery pipeline of novel therapeutic candidates based on proprietary knowledge of extracellular functions of tRNA synthetases (~300 protein compositions patented)

Lead Product Candidate: ATYR1923

Engineered, long acting, protein therapeutic, derived from the HARS gene, for the treatment of pulmonary sarcoidosis and other interstitial lung diseases

$2-3b[1] global opportunity

Financials:

Cash, cash equivalents and investments at $43m as of 3/31/2019

April 2019: $5m raise with Federated and Dr. Paul Schimmel, board member, at market, no discount or warrants

Clinical Milestones:

- ✓ Initiated P1b/2a Trial – 4Q 2018
- ❑ Interim Results – 4Q 2019
- ❑ Final Results – mid-2020[2]

(1) aTyr estimates for inflammatory ILD: Pulmonary Sarcoidosis, CHP, CTD-ILD; excludes IPF

(2) Dependent on patient enrollment

aTyr

Thank You