Diffuse parenchymal lung disease from sarcoidosis to alphabet soup

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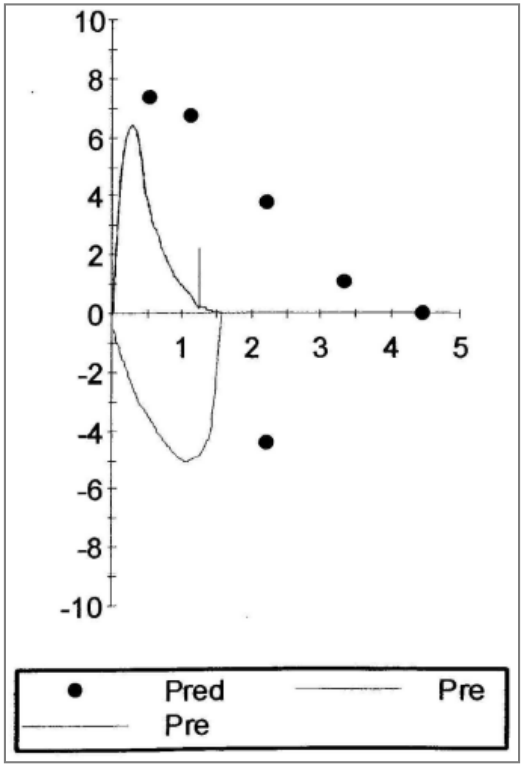
Disclosures

- Consulting/advisory
  - Boehringer-Ingelheim
  - Genentech
  - Gilead
  - Celgene
  - Araim
  - Mitsubishi-Tanabe
- Research support
  - Boehringer-Ingelheim
  - Mallinkrodt
  - Gilead
  - Araim
  - NHLBI
- No medication is FDA-approved for the other ILDs

A patient you are seeing…

A 59 year-old man presents with progressive dyspnea on exertion over the past one year. He reports a dry cough but no wheezes, sputum production, fevers or hemoptysis. He smoked 1 ppd for 20 years but quit 10 years ago. He works as a lawyer. PFTs are as follows:

Test	Actual	% Predicted
FEV_1	1.28	38
FVC	1.57	35
FEV_1/FVC	82	
TLC	2.70	42
DLCO	5.06	16

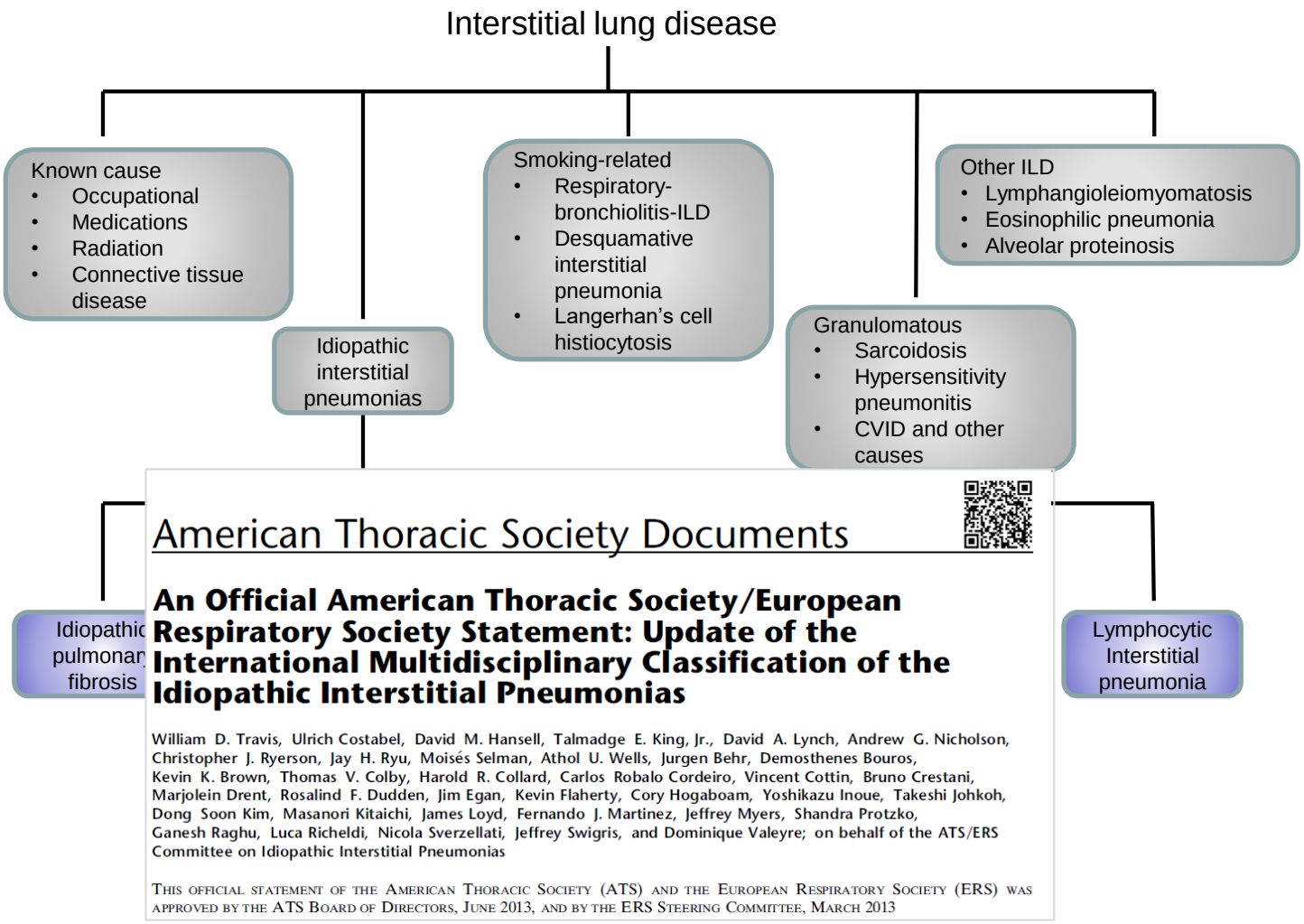


Is all UIP IPF?
What is CPFE? LAM?

Objectives

- Review the diagnostic approach and classification of ILD
- Update the pathogenesis and treatment of IPF
- Recognize the diagnostic dilemma encountered with IIPs
- Discuss sarcoidosis

Classifying ILD



Drug reactions are frequently missed

Which may be associated with obstruction as well as restriction?

- Idiopathic pulmonary fibrosis
- Sarcoidosis
- Asbestosis
- Combined pulmonary fibrosis-emphysema
- Scleroderma-ILD
- Lymphangioleiomyomatosis (LAM)
- Hypersensitivity pneumonitis
- Amiodarone lung

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Which are more likely to have exaggerated ↓FVC% < ↓DLCO%?

- Sarcoidosis
- IPF
- Hypersensitivity pneumonitis
- Rheumatoid lung
- Asbestosis
- Smoking-related ILD

Physical exam

- Non-specific
- Rales, squeaks, wheezes
- Connective tissue disease signs
- Lymph nodes
- Clubbing
- Cor pulmonale

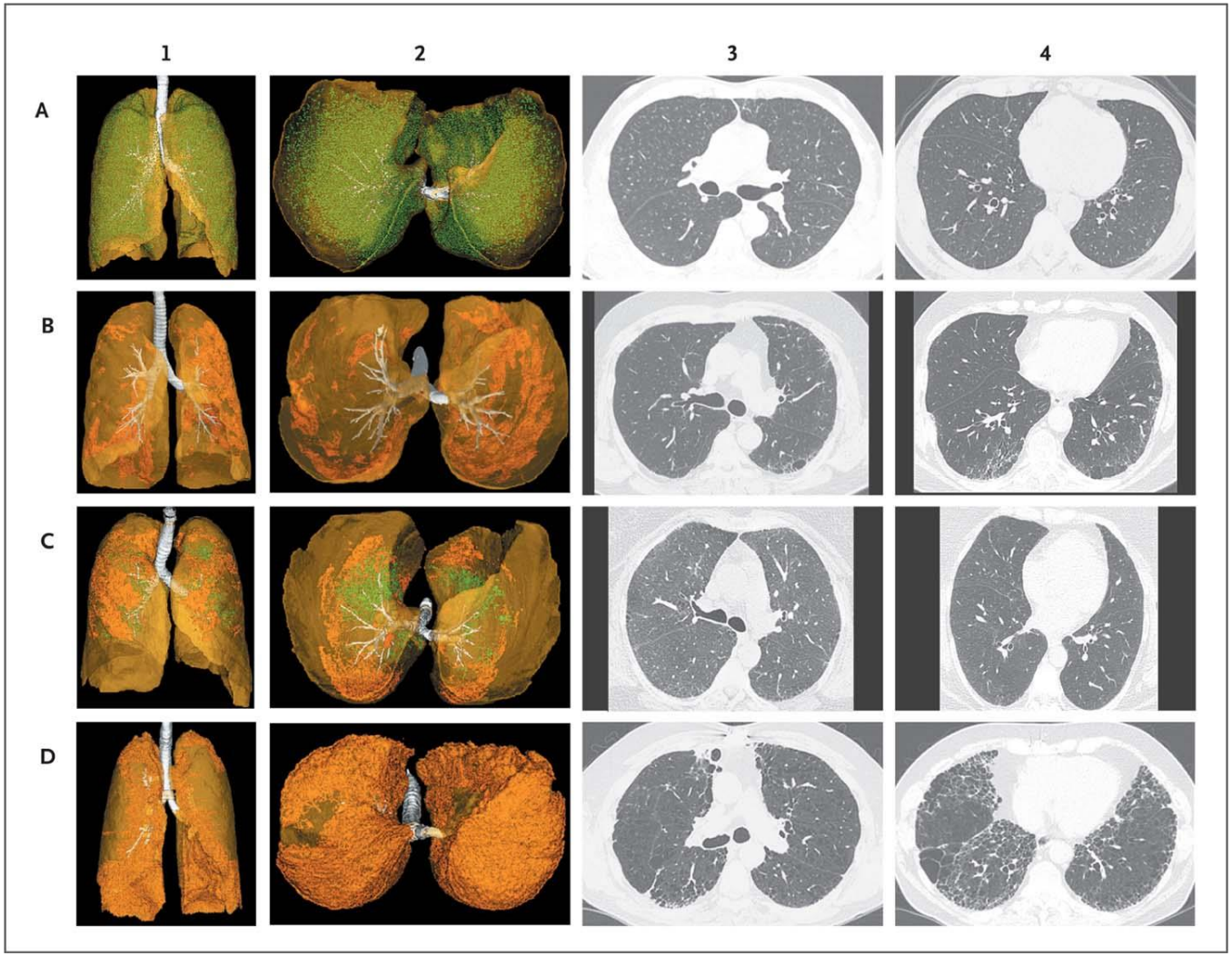
Interstitial Lung Abnormalities are present in 8-13%

Centrilobular

Subpleural

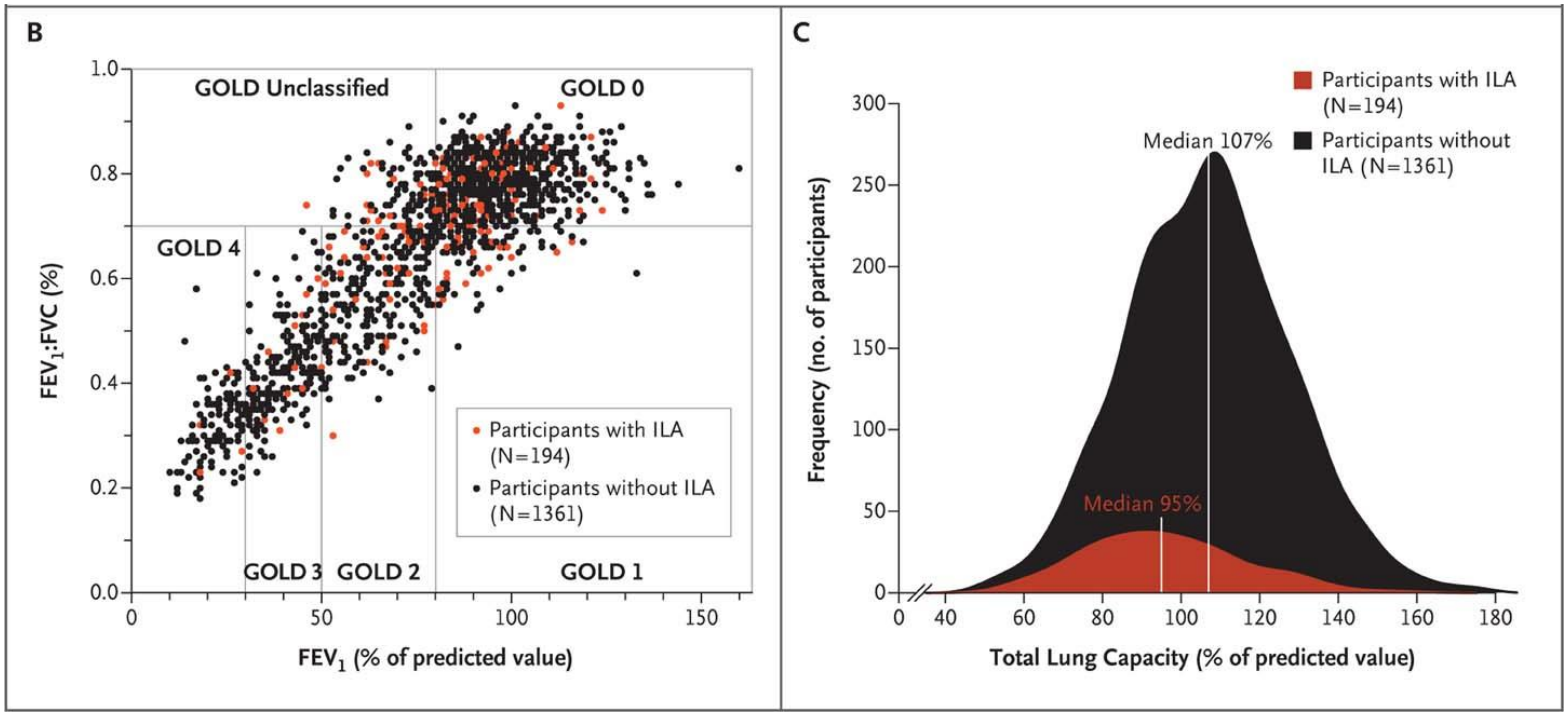
Mixed

Interstitial lung disease



Washko GR. N Engl J Med 2011

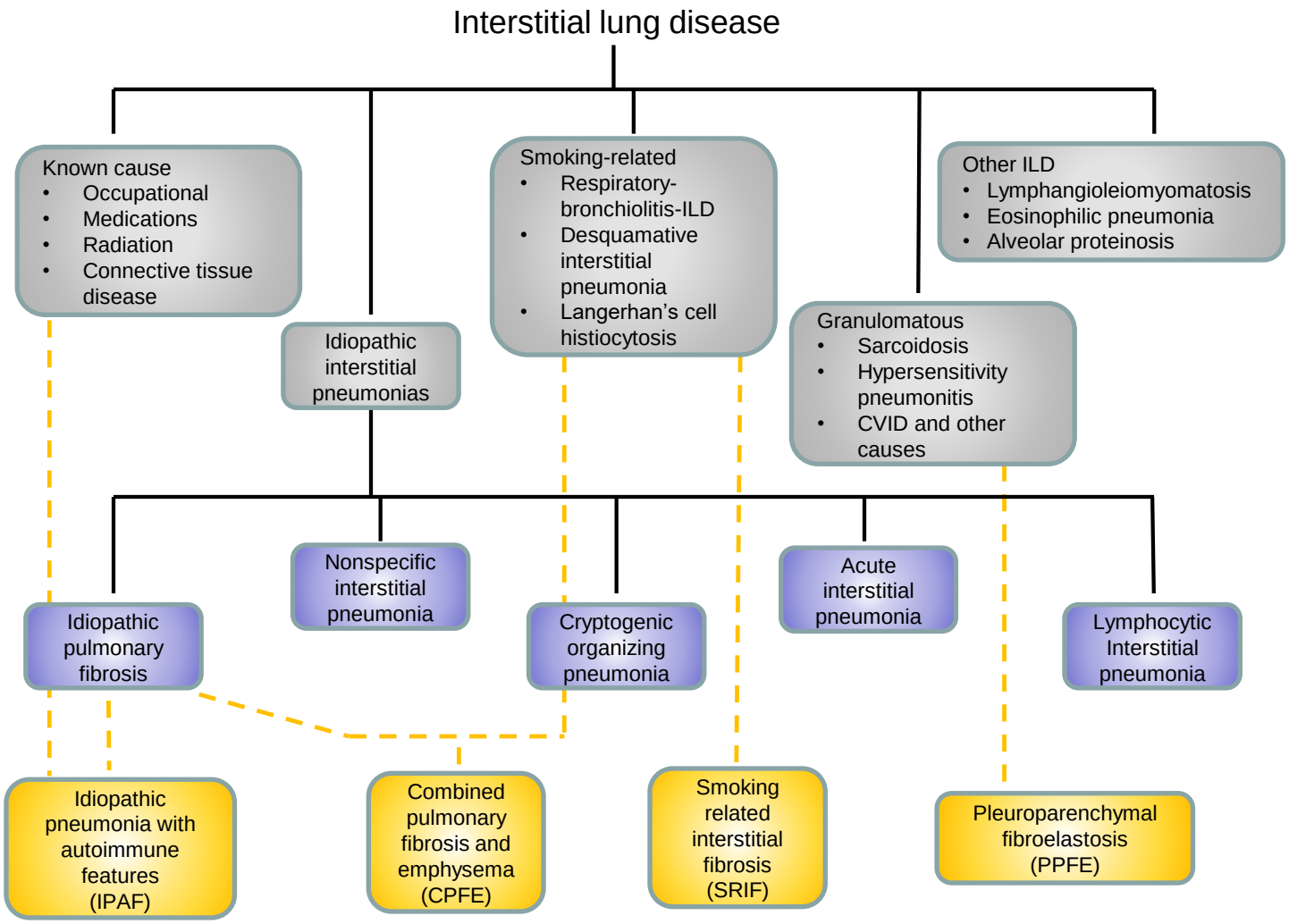
ILAs associate with pulmonary restriction



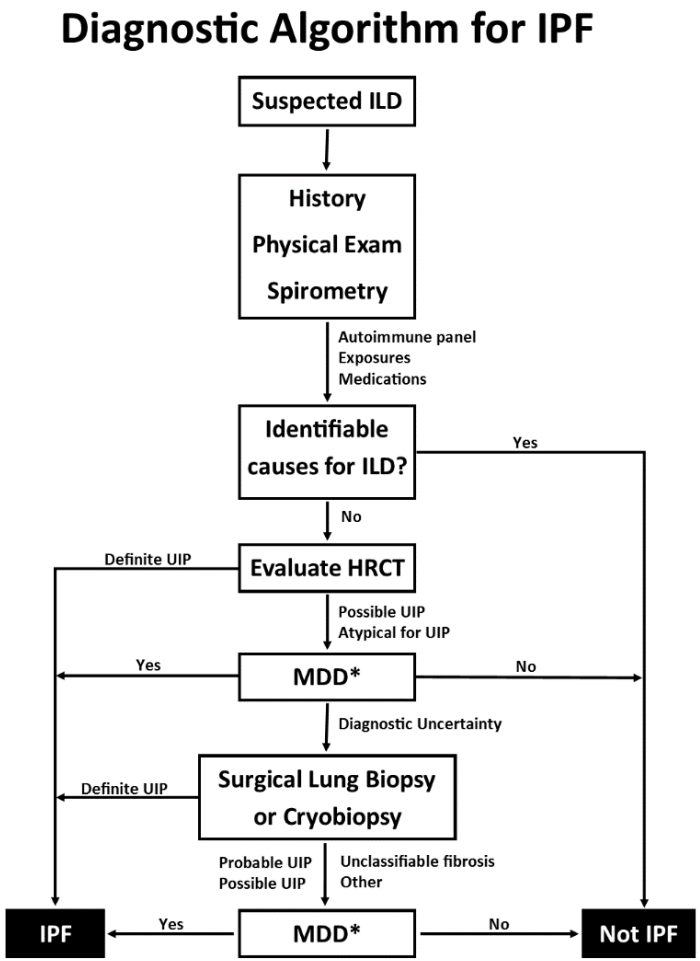
Washko GR. N Engl J Med 2011

Weekly multidisciplinary conference

“Job security”

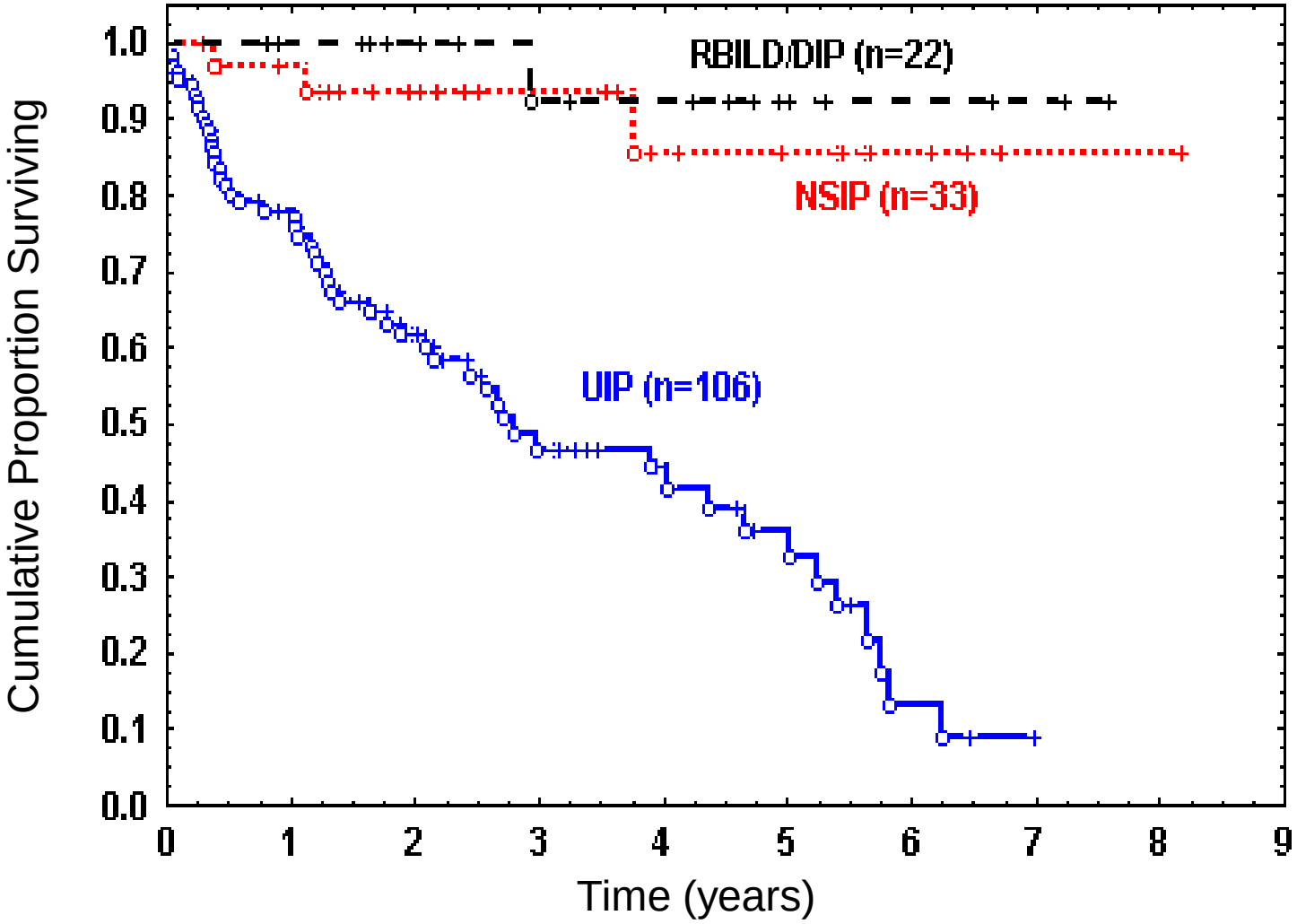


Practical approach for diagnosis of IPF

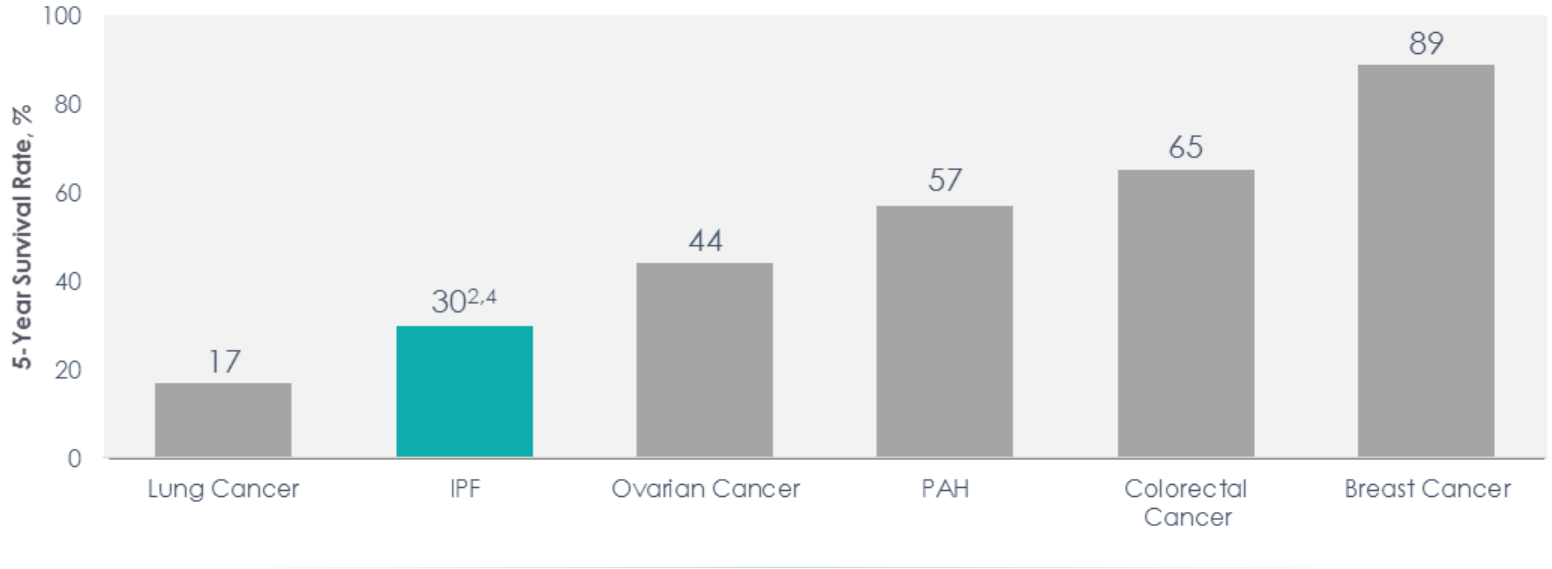


Tolle L. Cleve Clin J Med 2017.

IPF is worse than others



5-Year Survival Rate of IPF is Poor



Clinical prognostic factors per ATS

TABLE 7. SELECTED FEATURES ASSOCIATED WITH INCREASED RISK OF MORTALITY IN IDIOPATHIC PULMONARY FIBROSIS

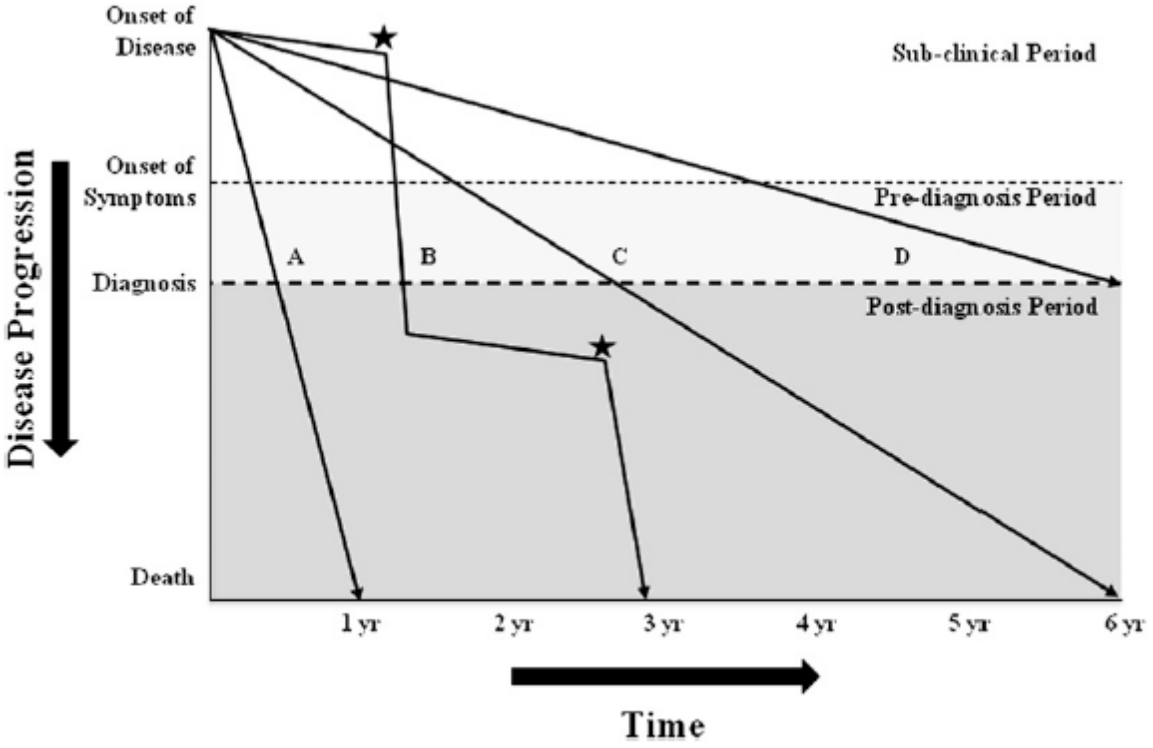
Baseline factors*
Level of dyspnea†
D_{LCO} < 40% predicted
Desaturation ≤ 88% during 6MWT
Extent of honeycombing on HRCT†
Pulmonary hypertension
Longitudinal factors
Increase in level of dyspnea†
Decrease in Forced Vital Capacity by ≥ 10% absolute value
Decrease in D_{LCO} by ≥ 15% absolute value
Worsening of fibrosis on HRCT†

Others include:

- Age
- Smoking
- Low BMI

Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, AJRCCM 2011

Variable course of IPF

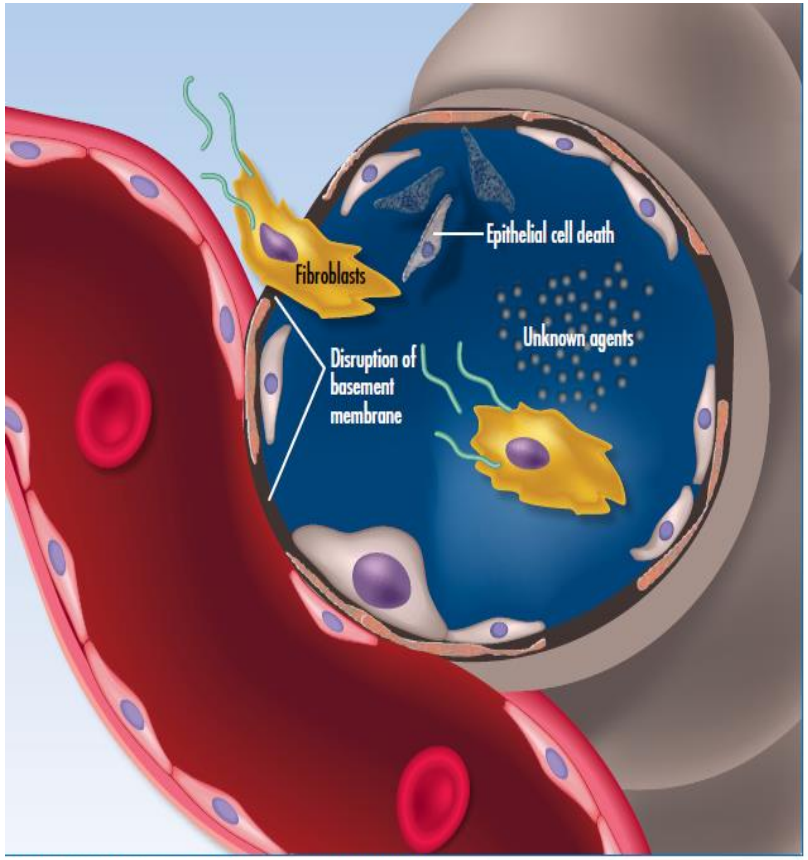


- Approximately 40,000 new cases per year in the U.S.
- 50,000/yr die from IPF

Raghu G. AJRCCM 2011.

Ley T. AJRCCM 2011.

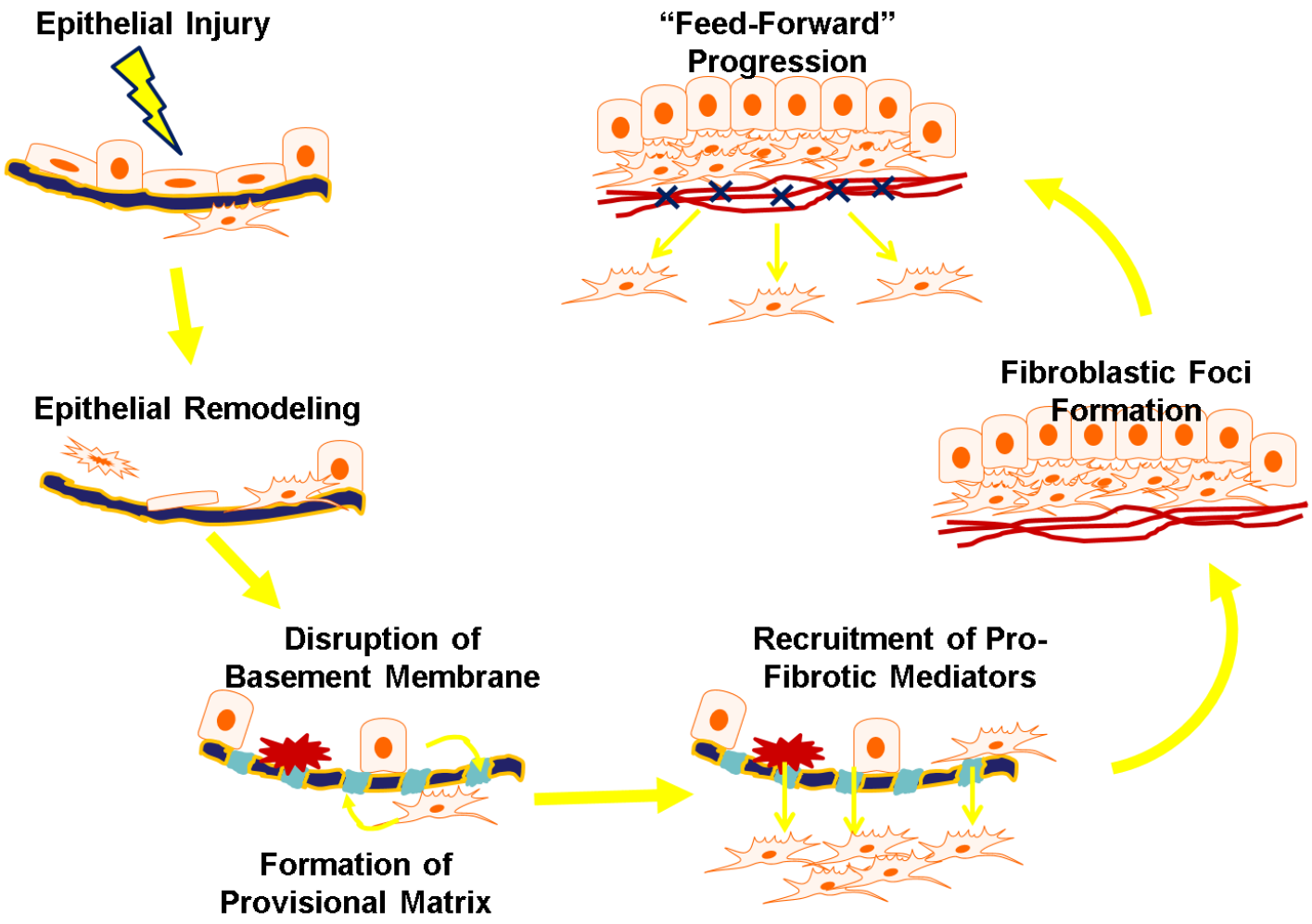
IPF Begins With an Initial Epithelial Injury



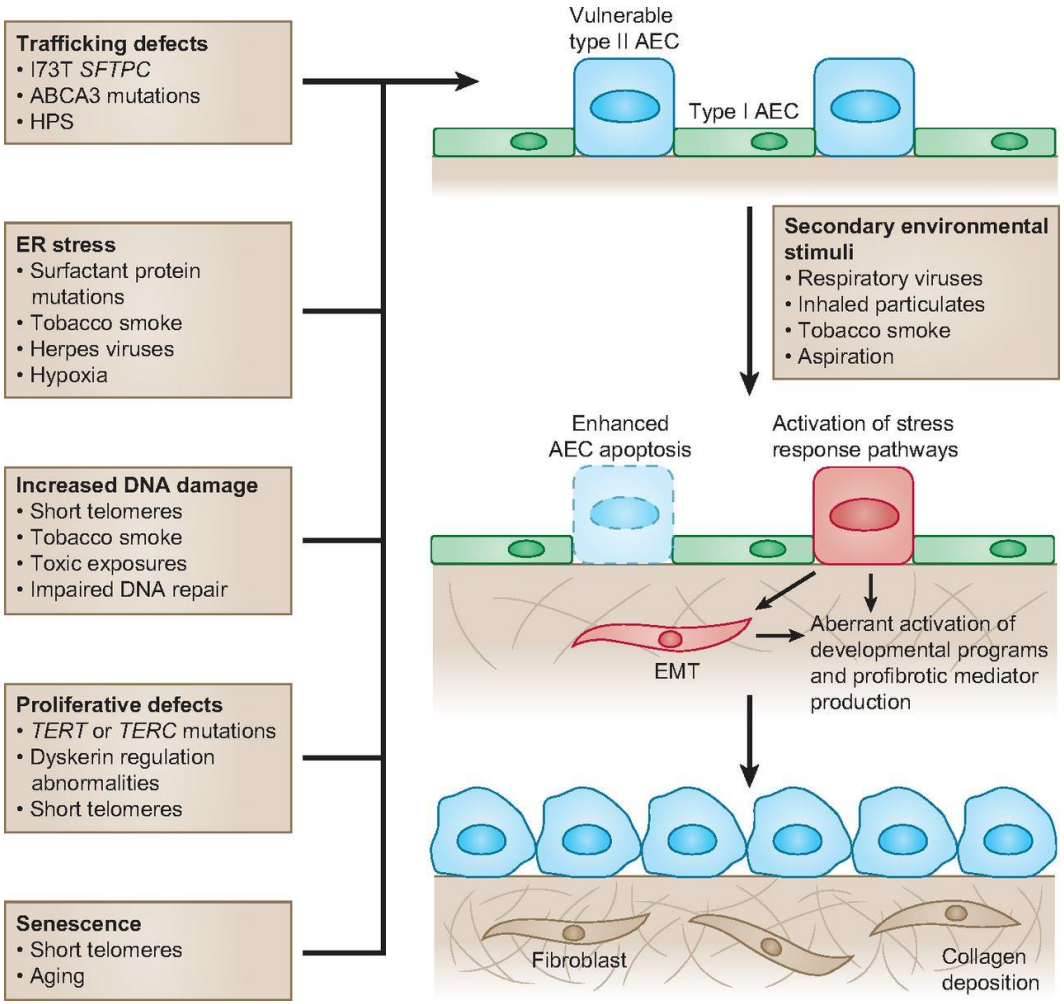
1. Injury of alveolar epithelial cells
2. Initiation of normal repair mechanisms
3. Release of profibrotic mediators into the alveolar space
4. Wound clot formation with inadequate epithelial repair

Image modified from: Selman M et al. Ann Intern Med 2001;134:136–151.

Pathogenesis of IPF

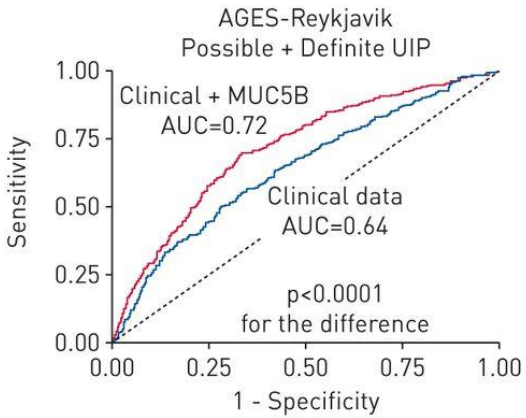


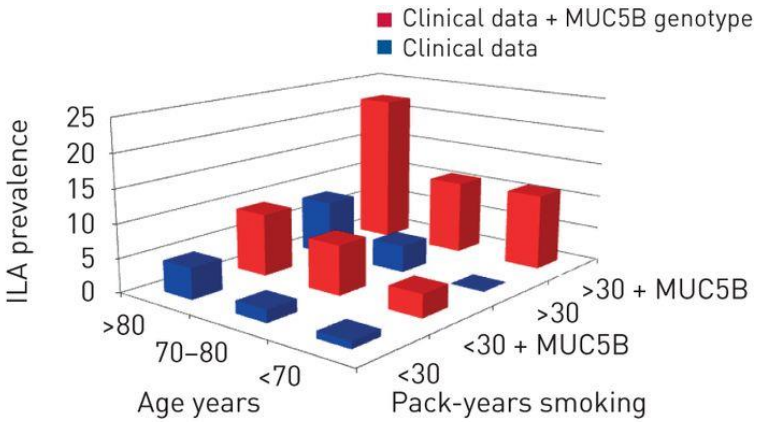
Genetic influencers of fibrosis

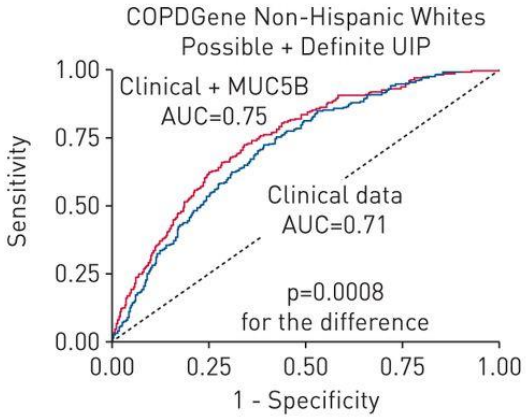


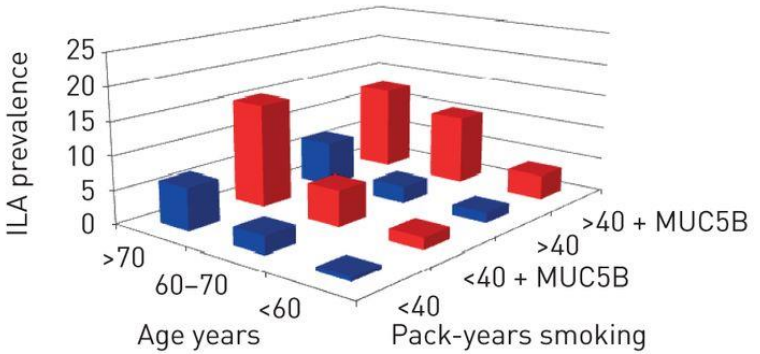
Kropski JA. Dis Model Mech 2013

MUC5B promoter polymorphism and risk of UIP pattern in ILAs



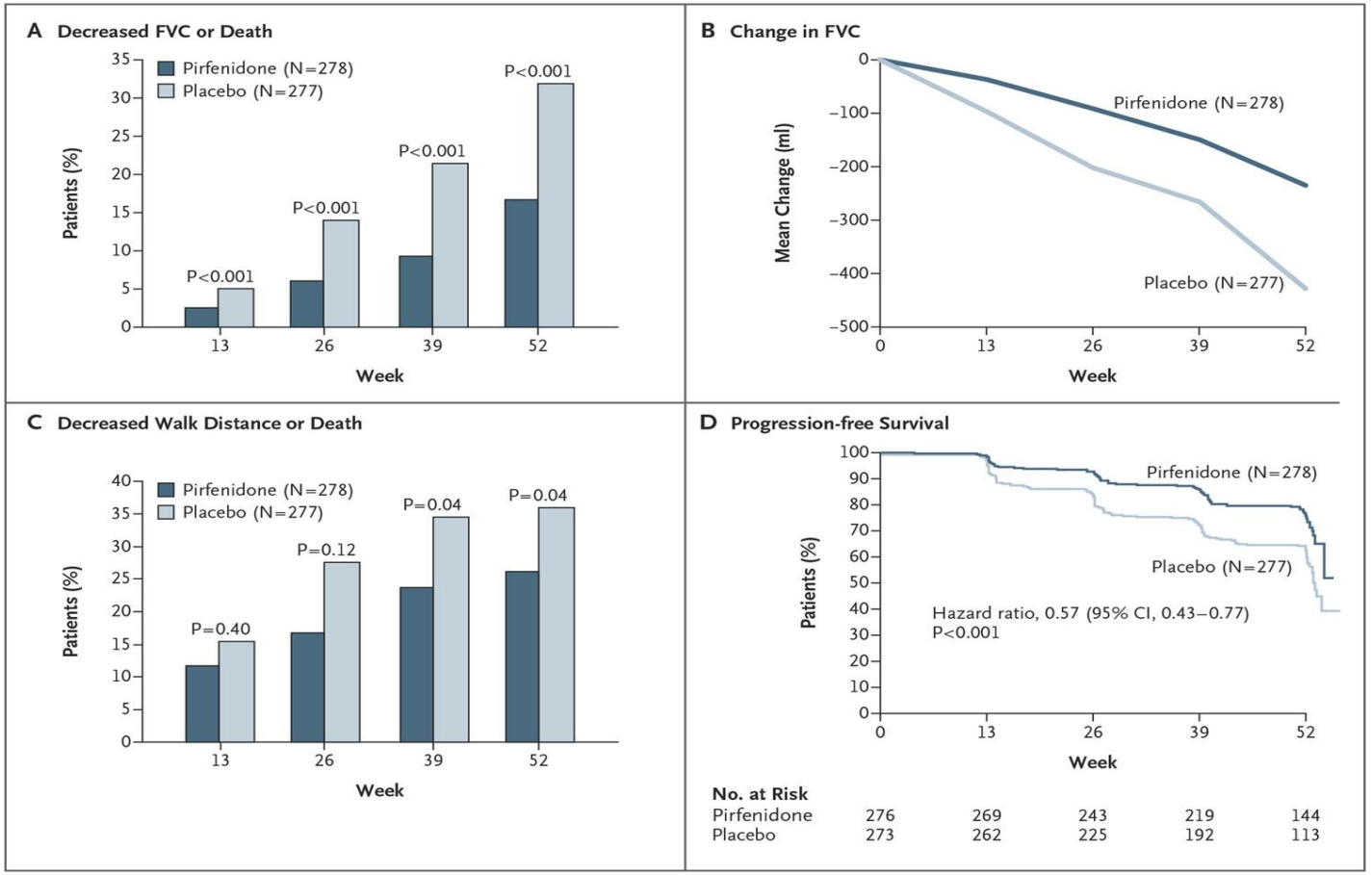






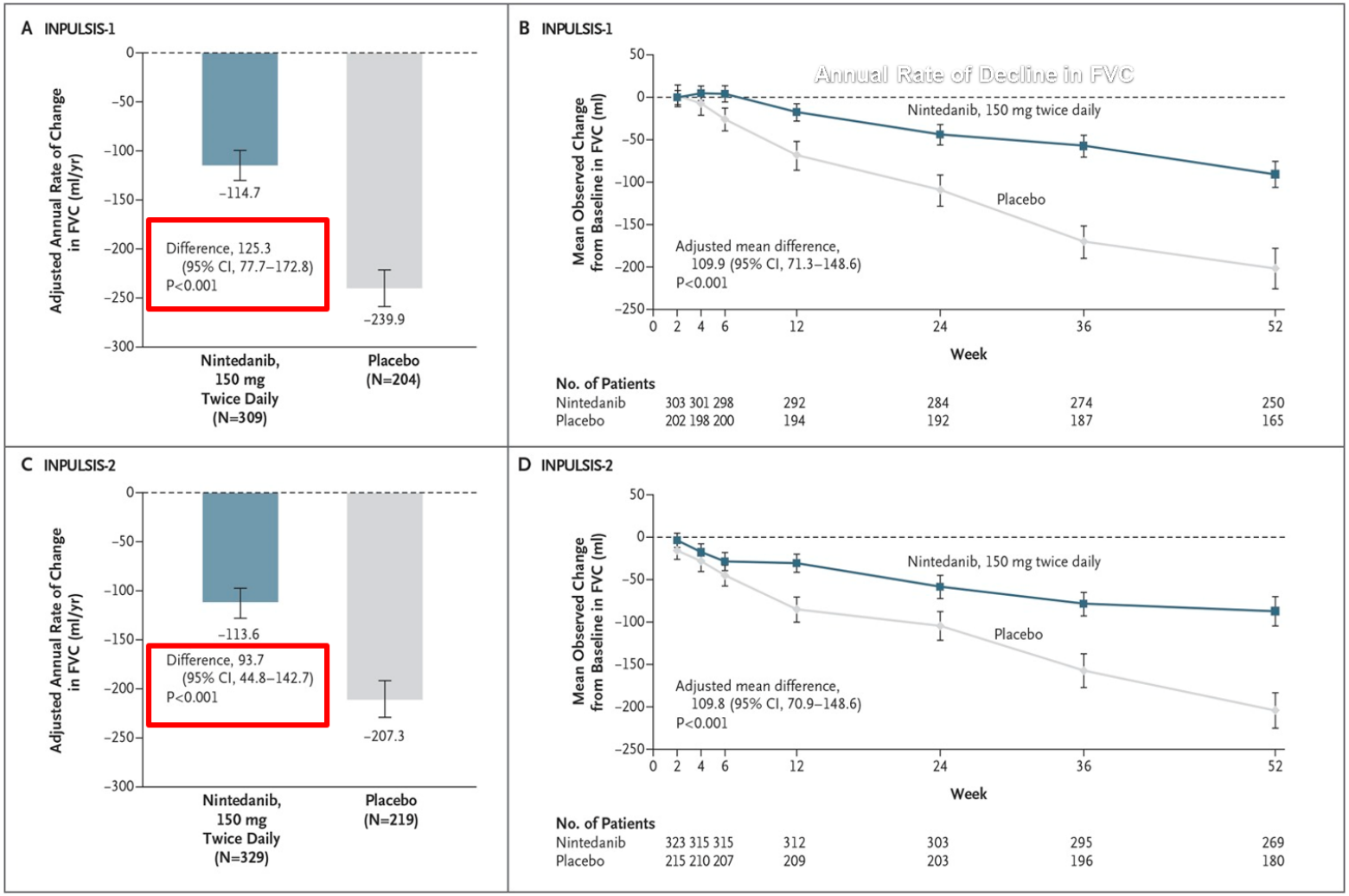
Putman RK. Eur Respir J 2017

ASCEND trial: pirfenidone for IPF

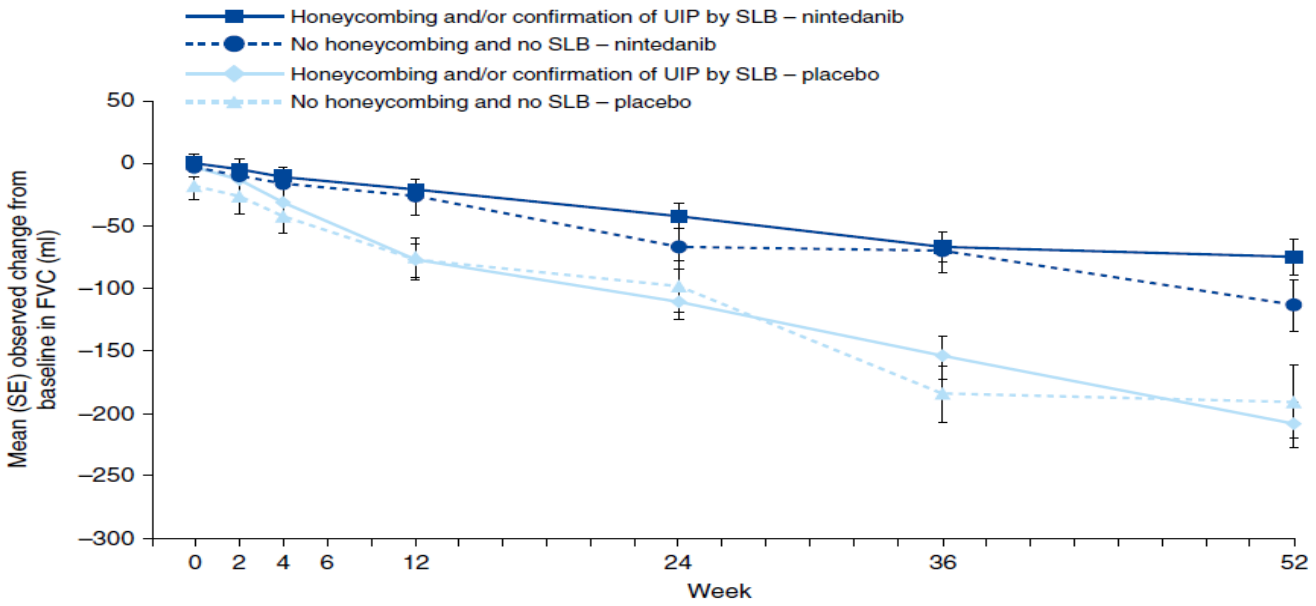


King TE. N Engl J Med 2014

INPULSIS trials: nintedanib



Is possible UIP just occult definite UIP?



No of patients							
Honeycombing and/or confirmation of UIP by SLB - nintedanib	418	409	408	398	385	377	341
No honeycombing and no SLB - nintedanib	208	207	205	206	202	192	178
Honeycombing and/or confirmation of UIP by SLB - placebo	293	289	291	284	275	267	239
No honeycombing and no SLB - placebo	124	119	116	119	120	116	106

Figure 3. Change from baseline in FVC over time by subgroup. SLB = surgical lung biopsy; UIP = usual interstitial pneumonia.

Raghu G. AJRCCM 2017

IPF therapy

Good ideas

- Pulmonary rehabilitation
- Oxygen supplementation
- Find comorbidities
  - OSA
  - GER
  - Depression
- “The lungs can’t take a joke”—hygiene and vaccines

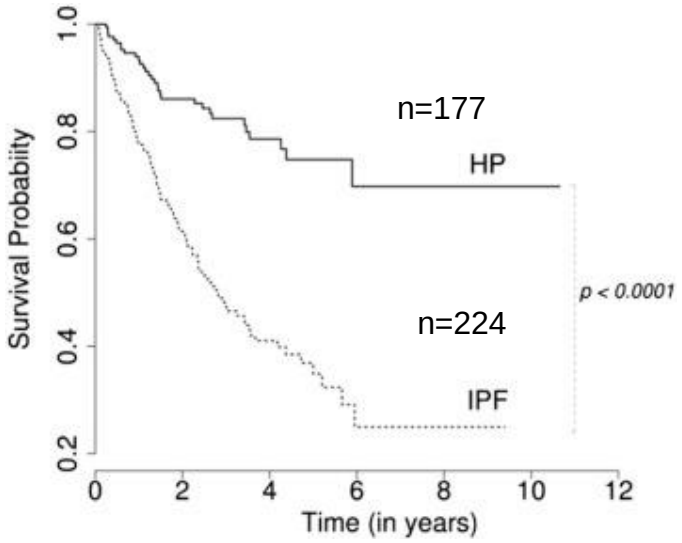
Bad ideas

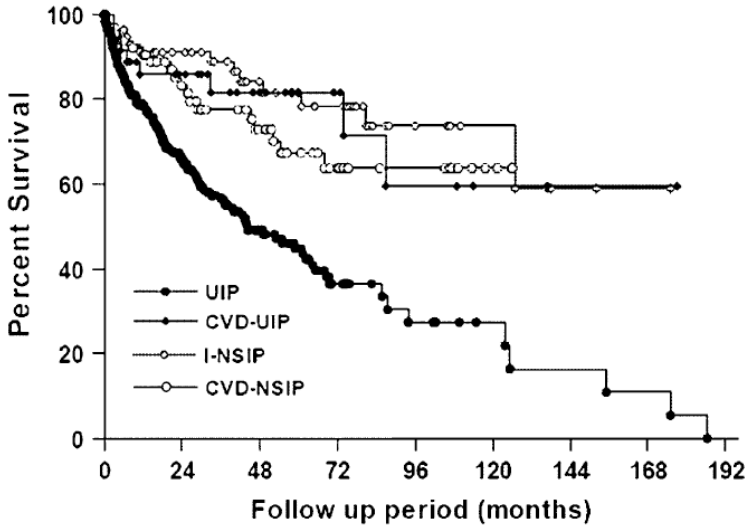
- Prednisone
- Immunosupressants
- PAH treatment?
- High Vt ventilation

Interim summary: IPF

- Most common and most devastating ILD
- Think of it in older males, especially with exposures
- Acute exacerbations may be idiopathic or not
- 5-10% FVC decline, 10-15% DLCO decline, worsened oxygenation are tip-offs for poor outcomes
- More pulmonary rehab
- “Interstitial lung abnormalities”…

Etiology and histopathology both influence the outcome





Mooney JJ. Chest 2013

Park JH. Am J Respir Crit Care Med 2007

HP is a common cause of occupational lung disease

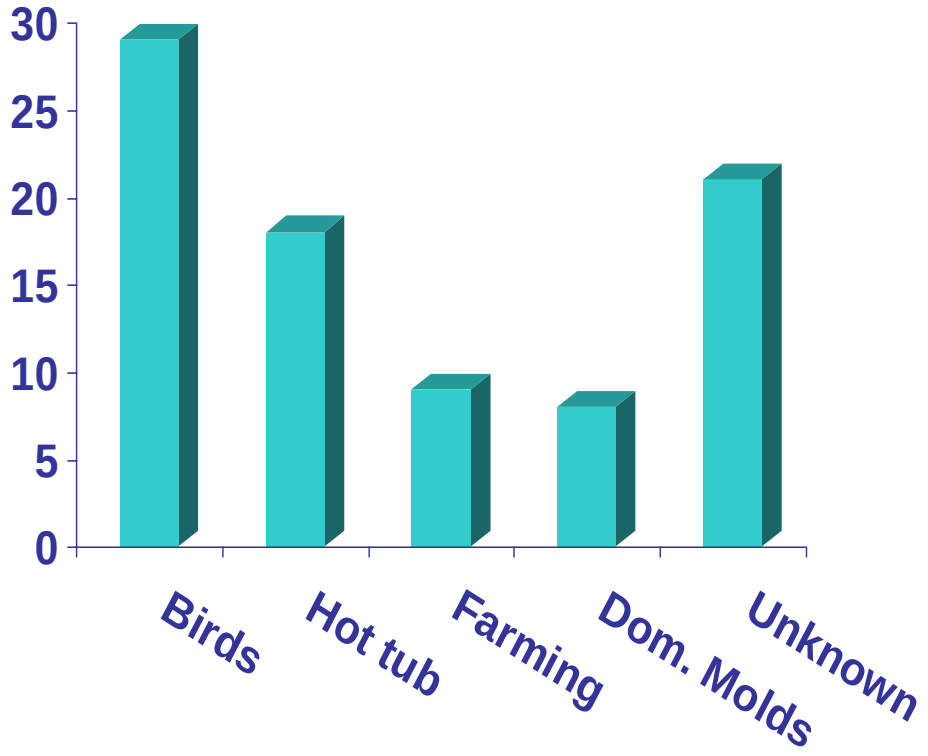
"Almost all who make a living by sifting or measuring grain are short of breath and cachectic and rarely reach old age."

-*Morbis Artificum Diatriba*

Hypersensitivity pneumonitis syndrome

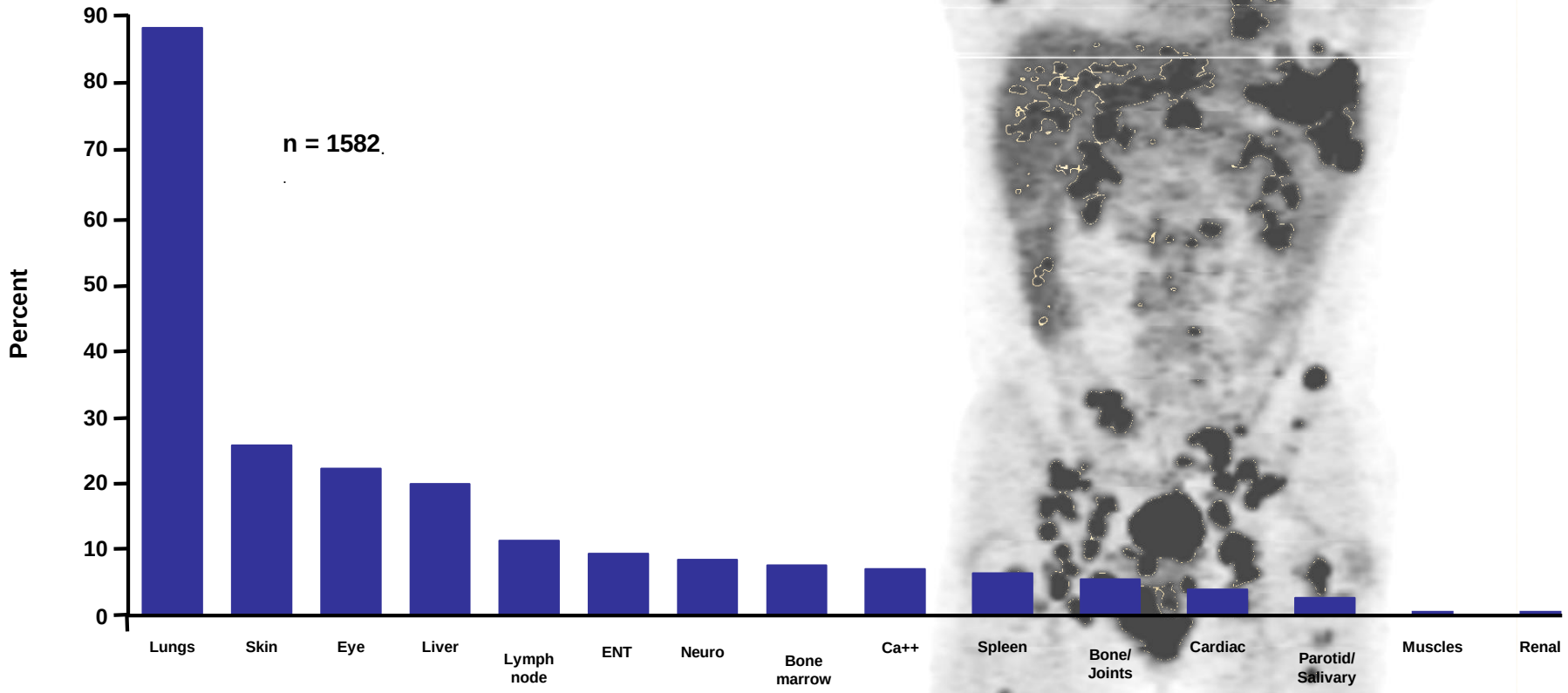
Usually due to inhaled antigens (≤ 5µm)

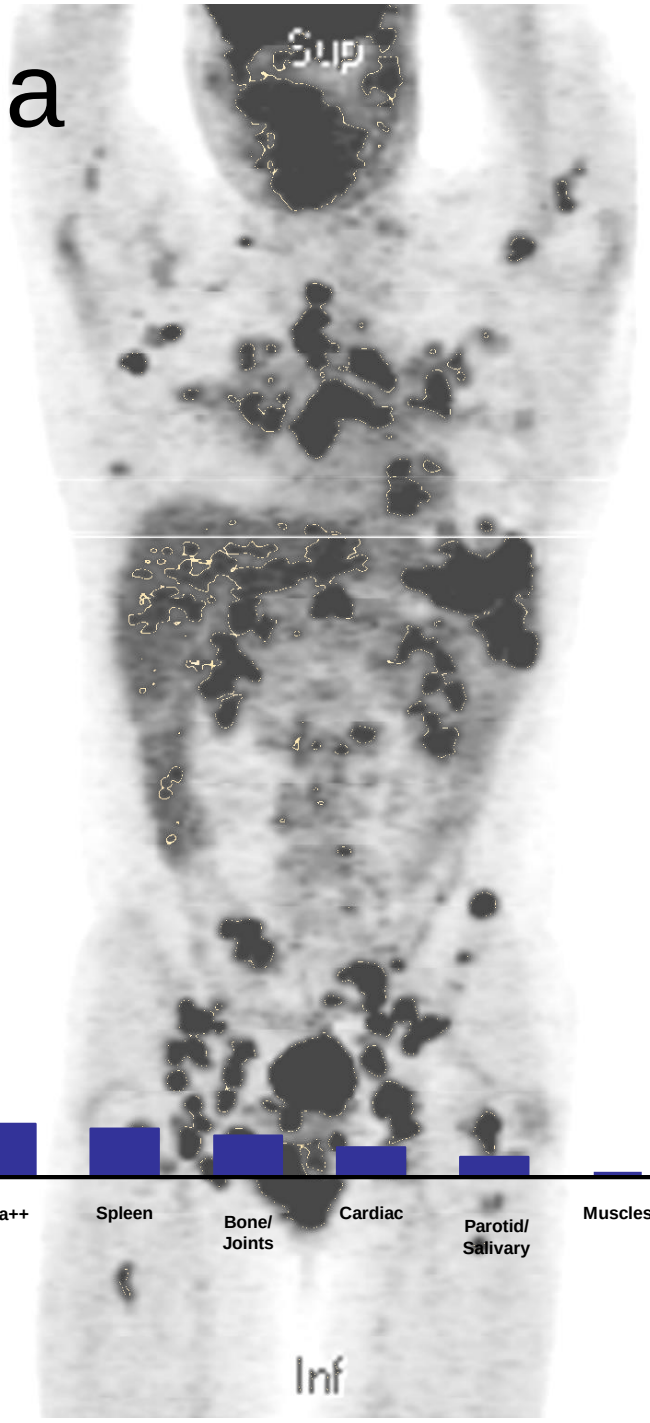
- Animal proteins
- Micro-organisms
- Hydrocarbons (e.g. isocyanates)



Hanak V. Mayo Clin Proc 2007

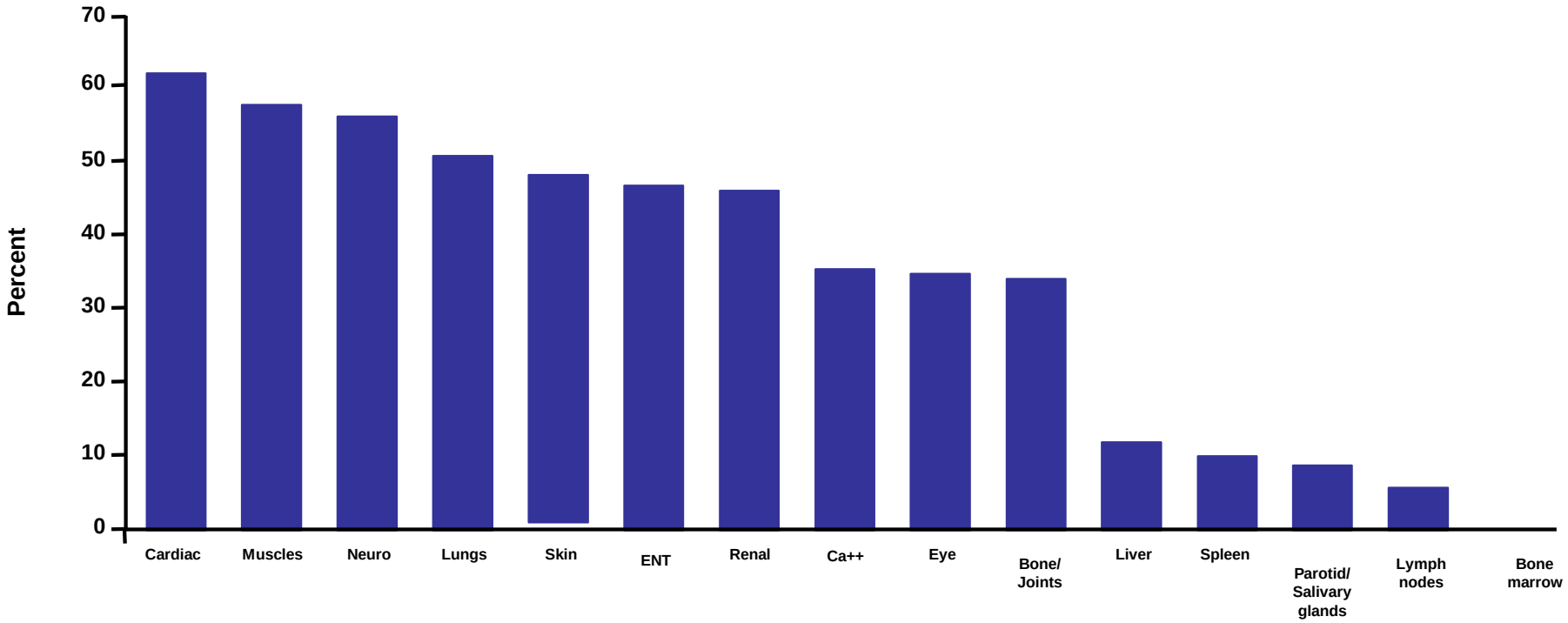
Organ involvement in a US sarcoidosis clinic





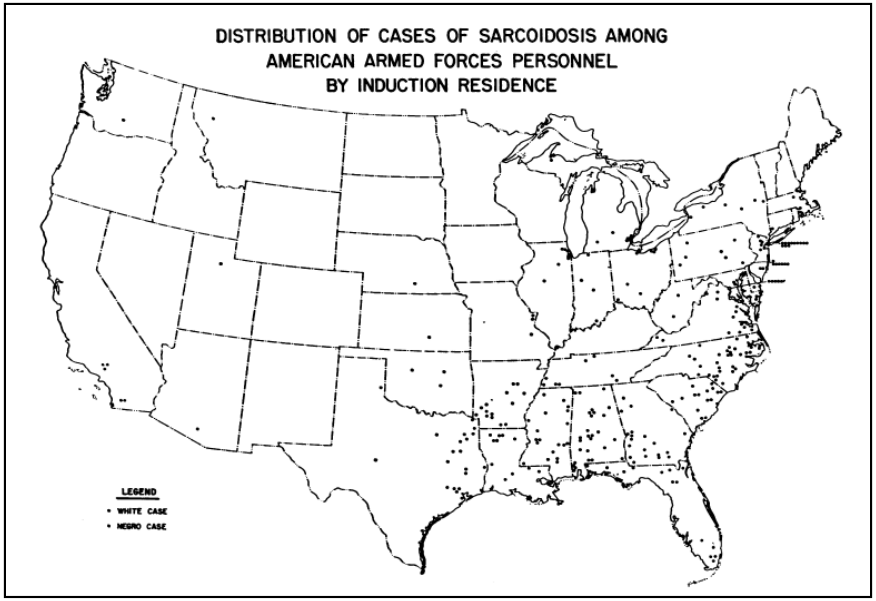
Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012

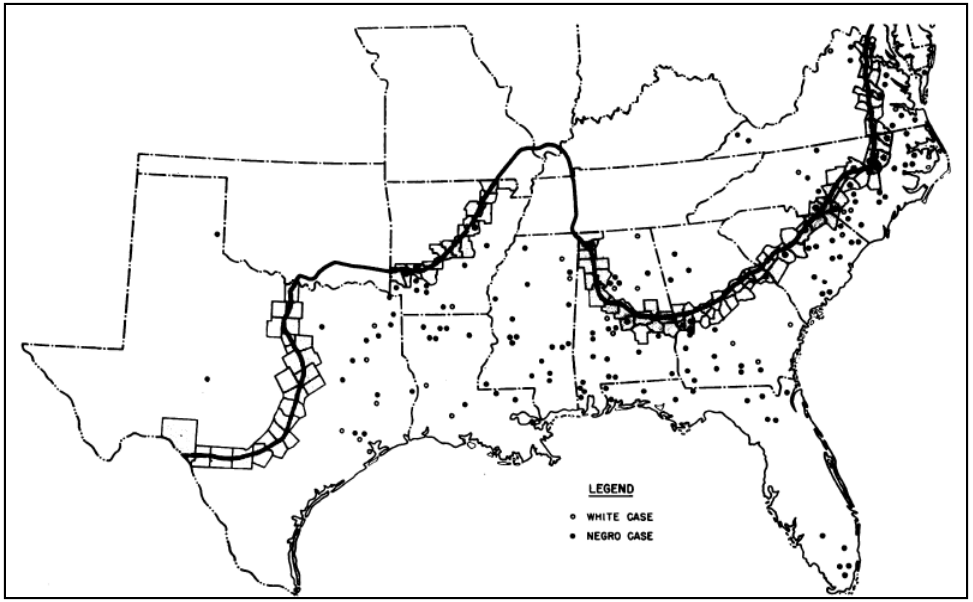
Frequency of treatment requirement



Judson MA. Sarcoidosis Vasc Diffuse Lung Dis 2012

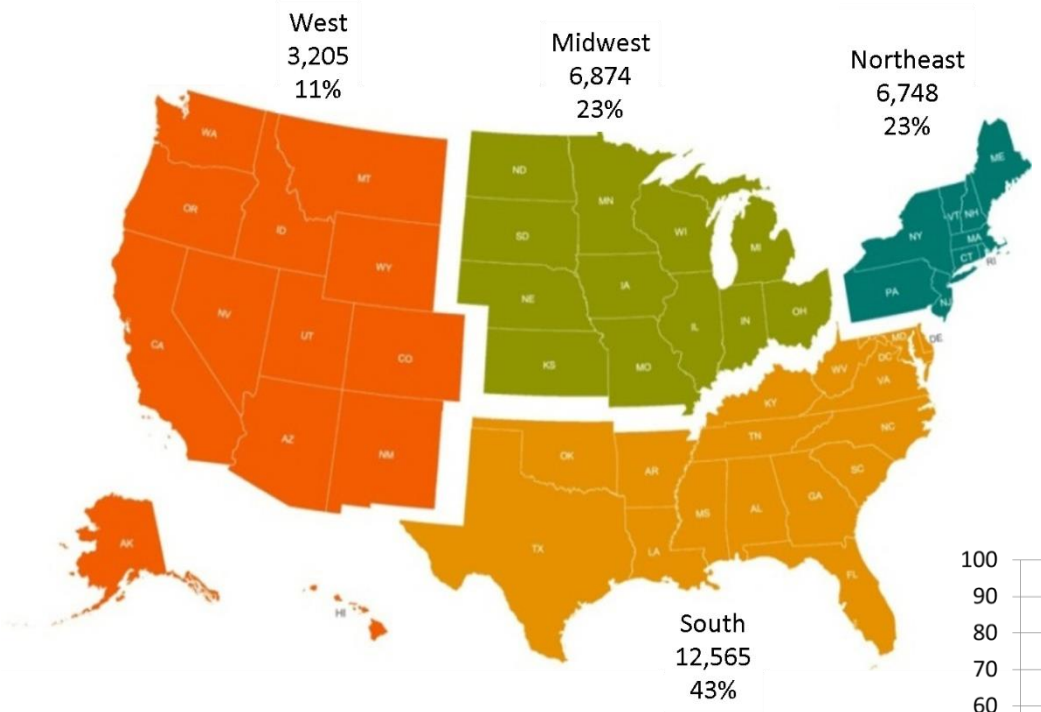
Sarcoidosis in US military personnel during WWII

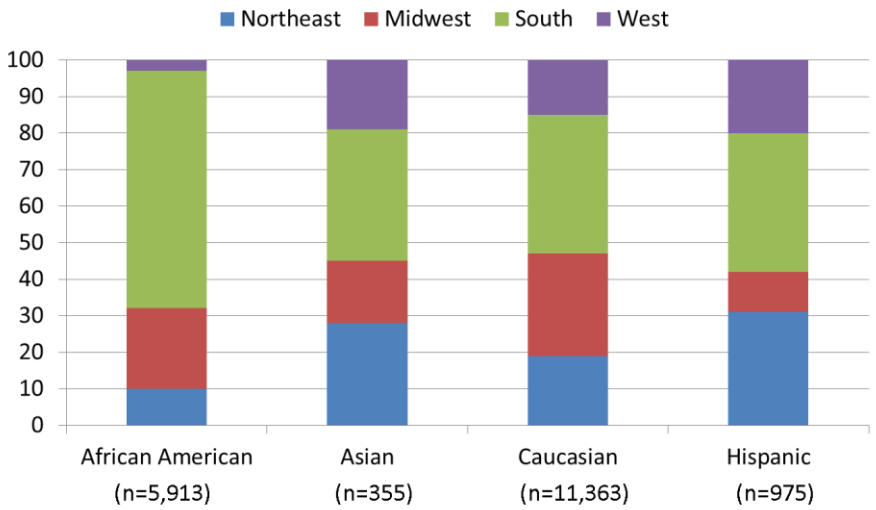




Gentry J Clin Invest 1955

Sarcoidosis more common in the Southeast

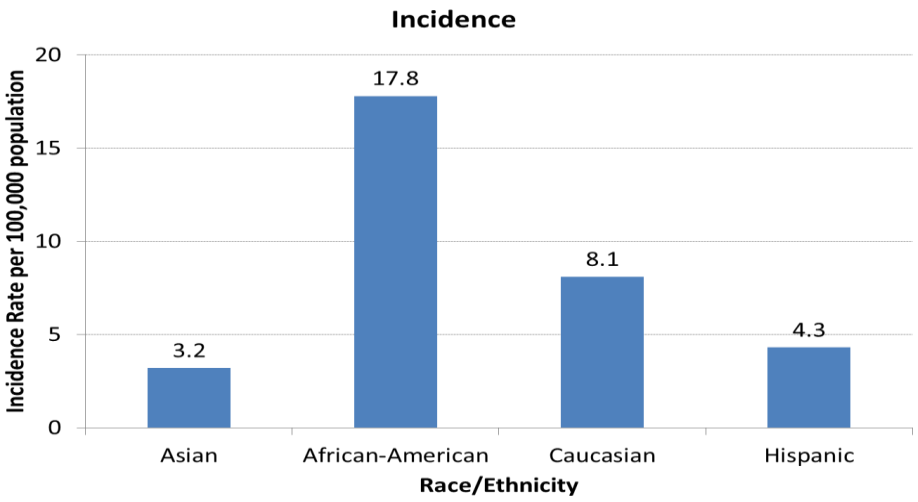


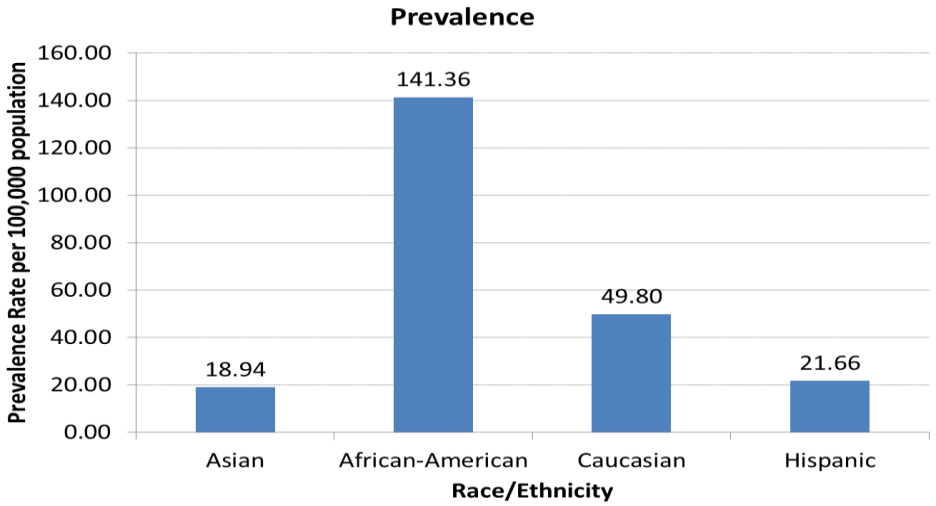


Baughman RP. Ann Am Thorac Soc 2016

Sarcoidosis in the US

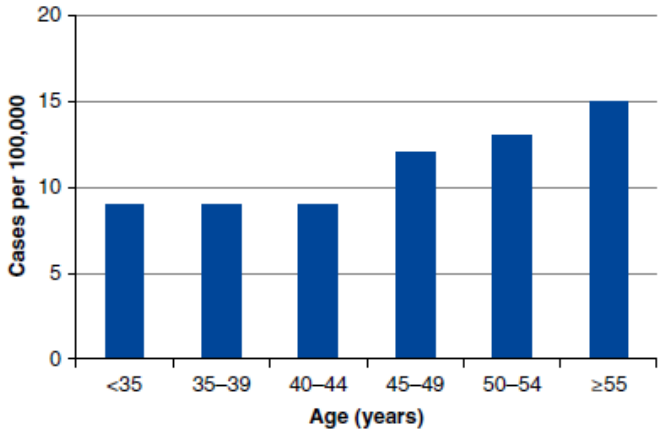
2010-2013 Optum Database

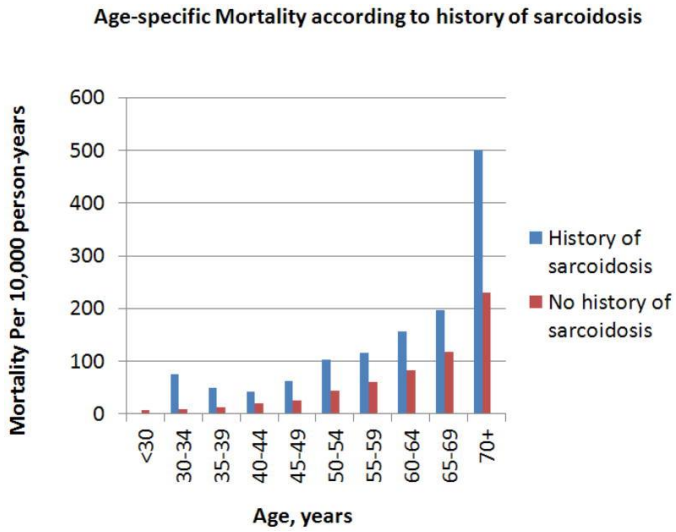


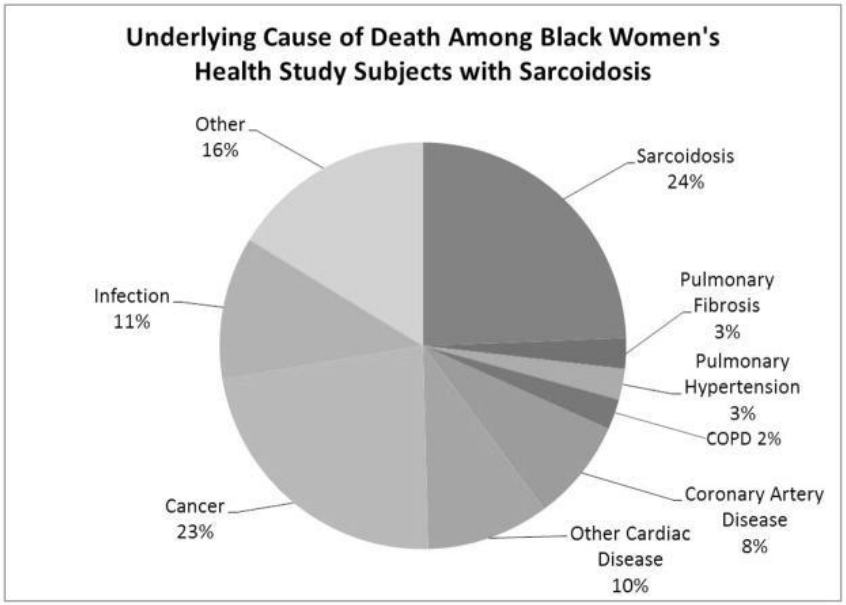


Baughman RP. Ann Am Thorac Soc 2016

Upward age shift



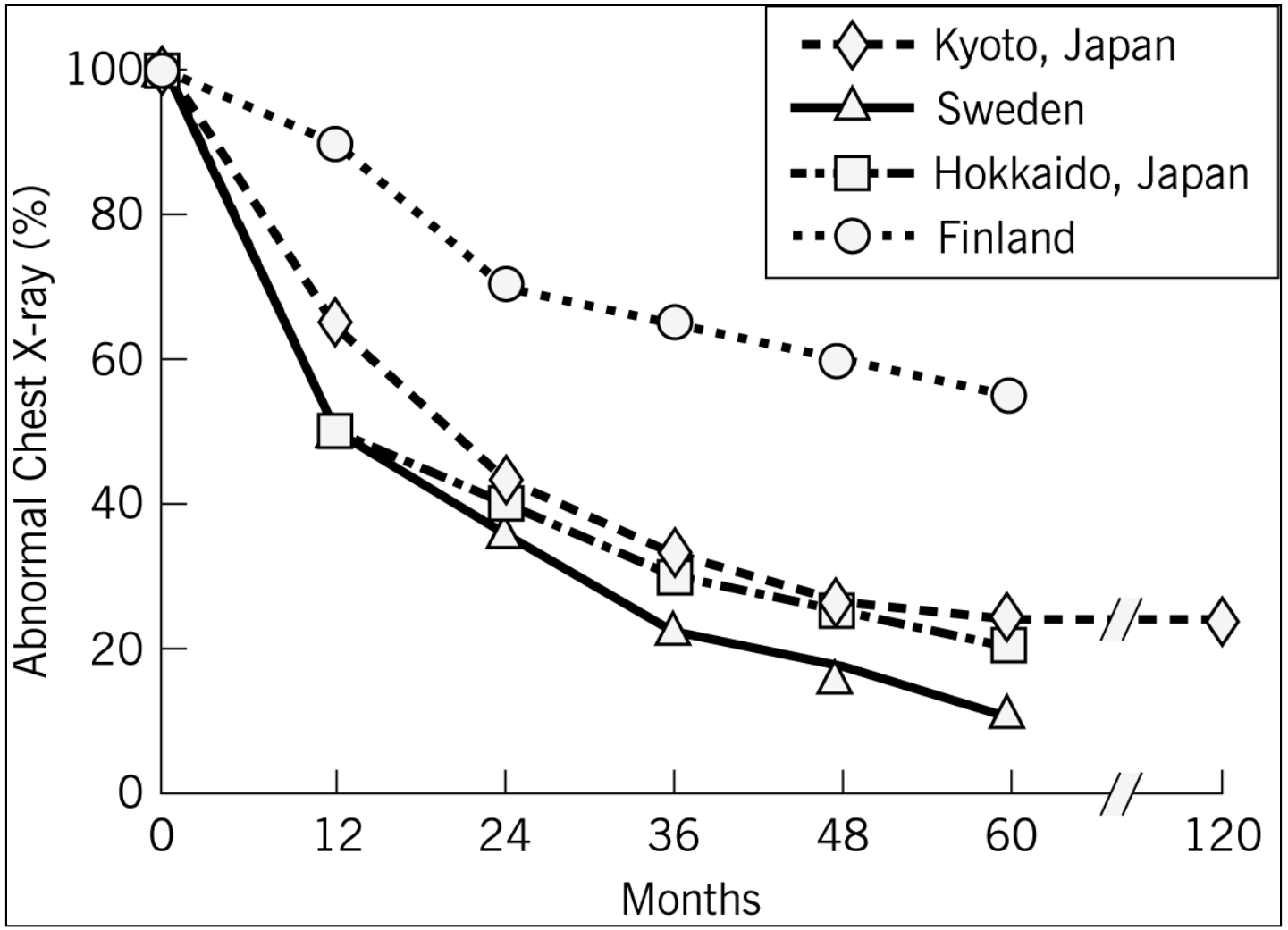




Dumas O. Ann Am Thorac Soc 2016

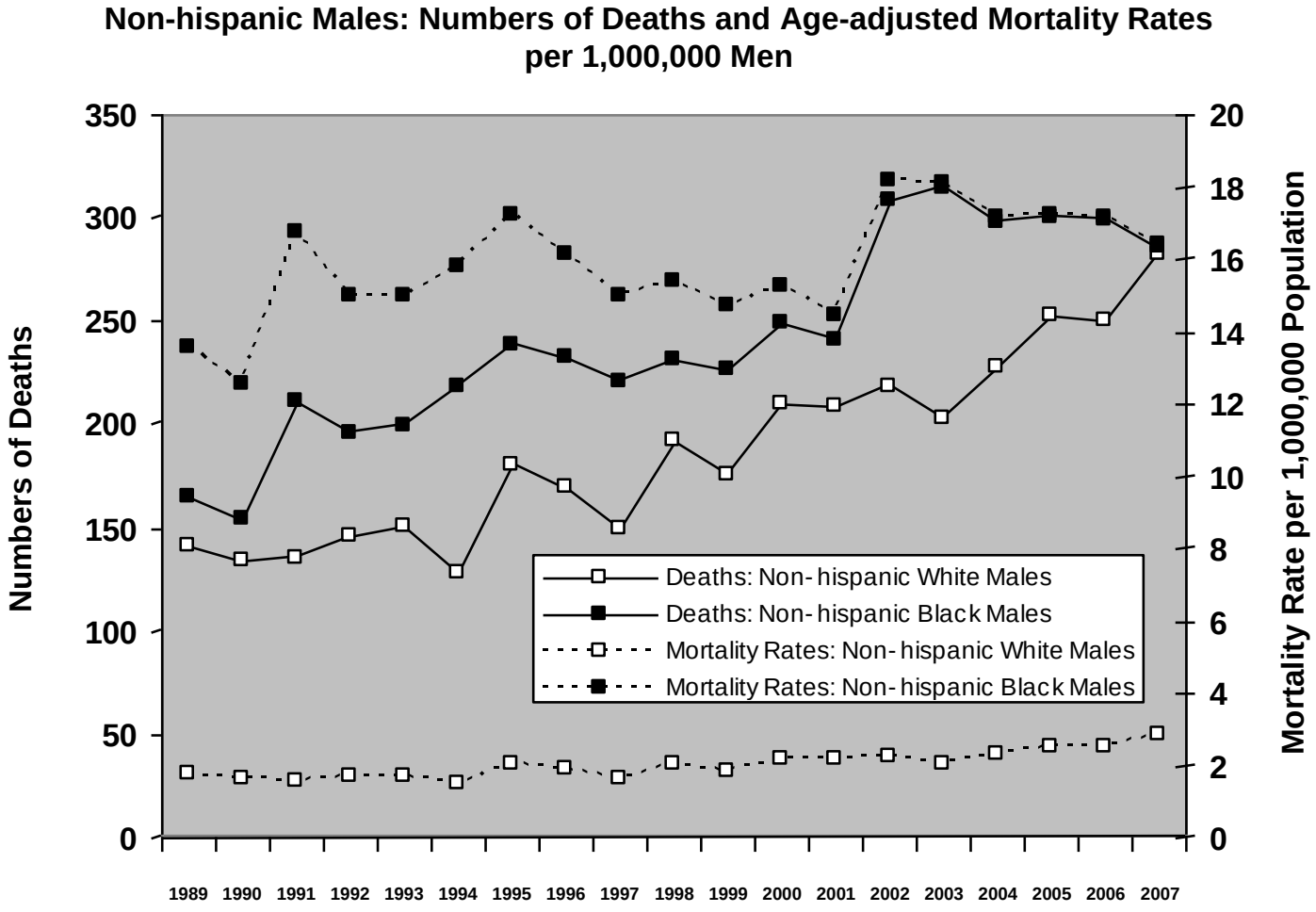
Tukey MH. Sarcoidosis Vasc Diffuse Lung Dis 2013

Many individuals resolve their CXR



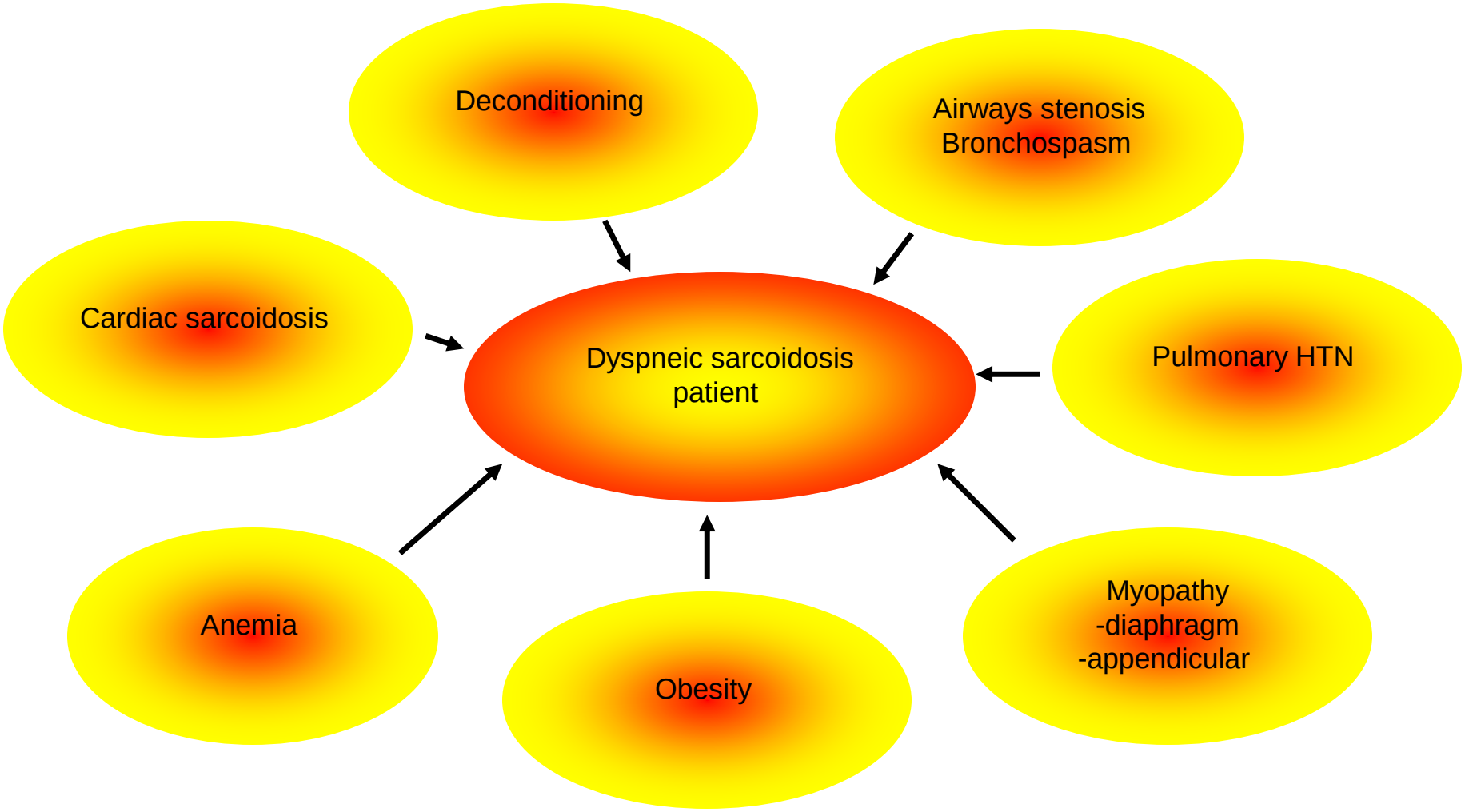
Lazar CA. Sem Respir Crit Care Med 2010

Rising sarcoidosis mortality in the US

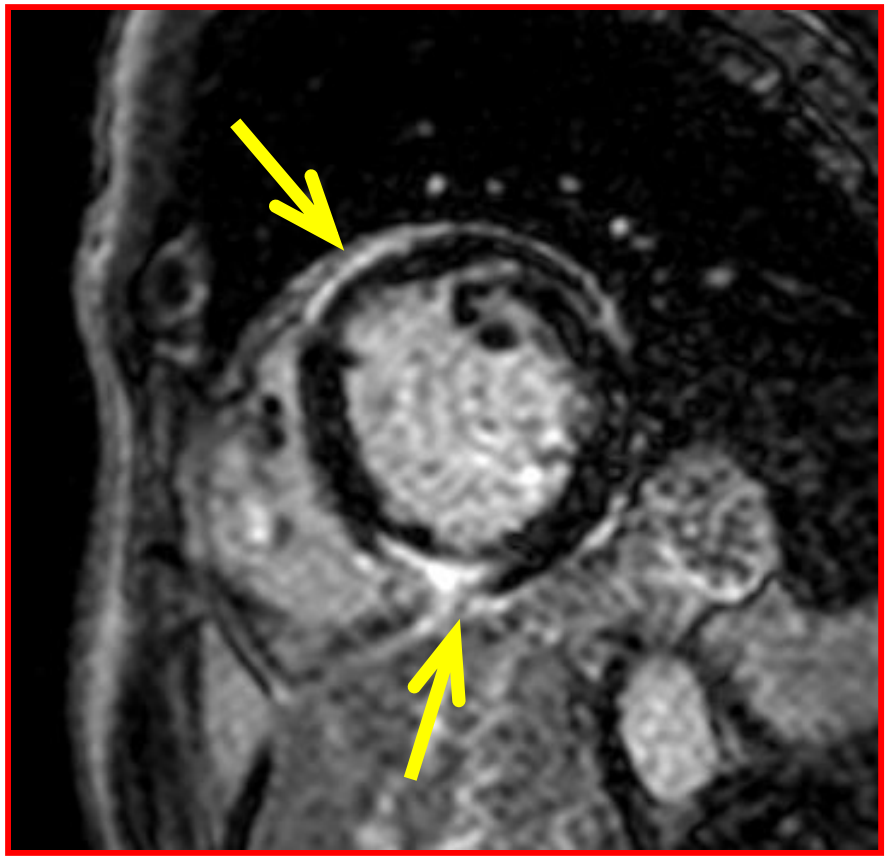


Swigris JJ. AJRCCM 2011

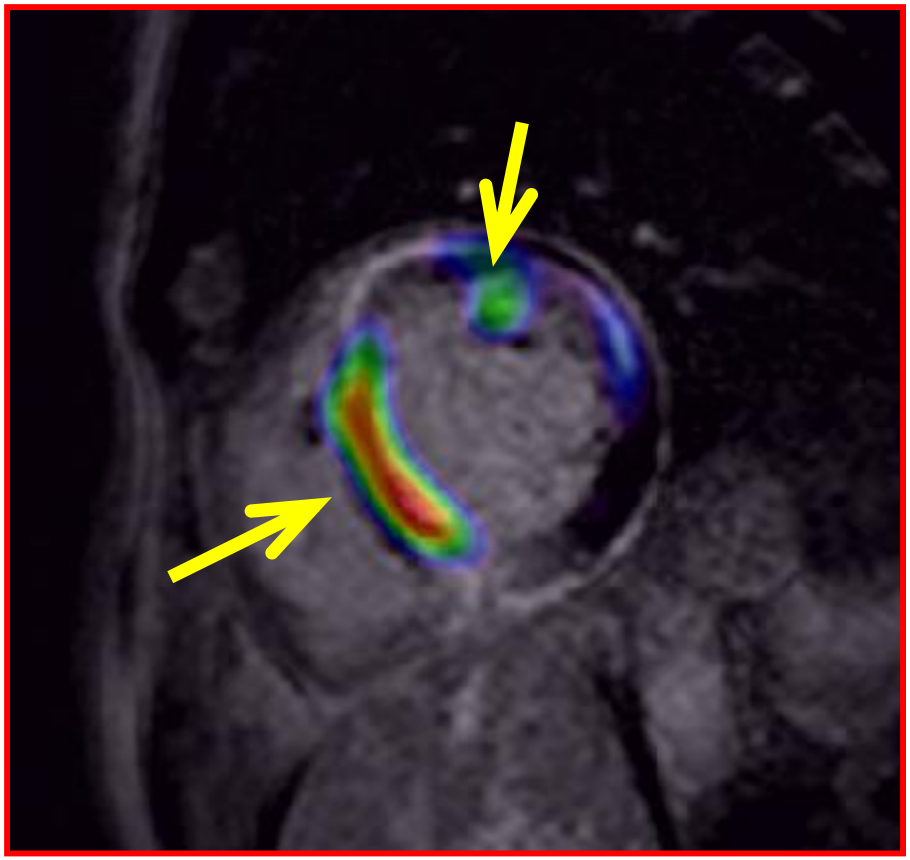
Multifaceted dyspnea of sarcoidosis



Cardiac sarcoidosis



DE-MRI

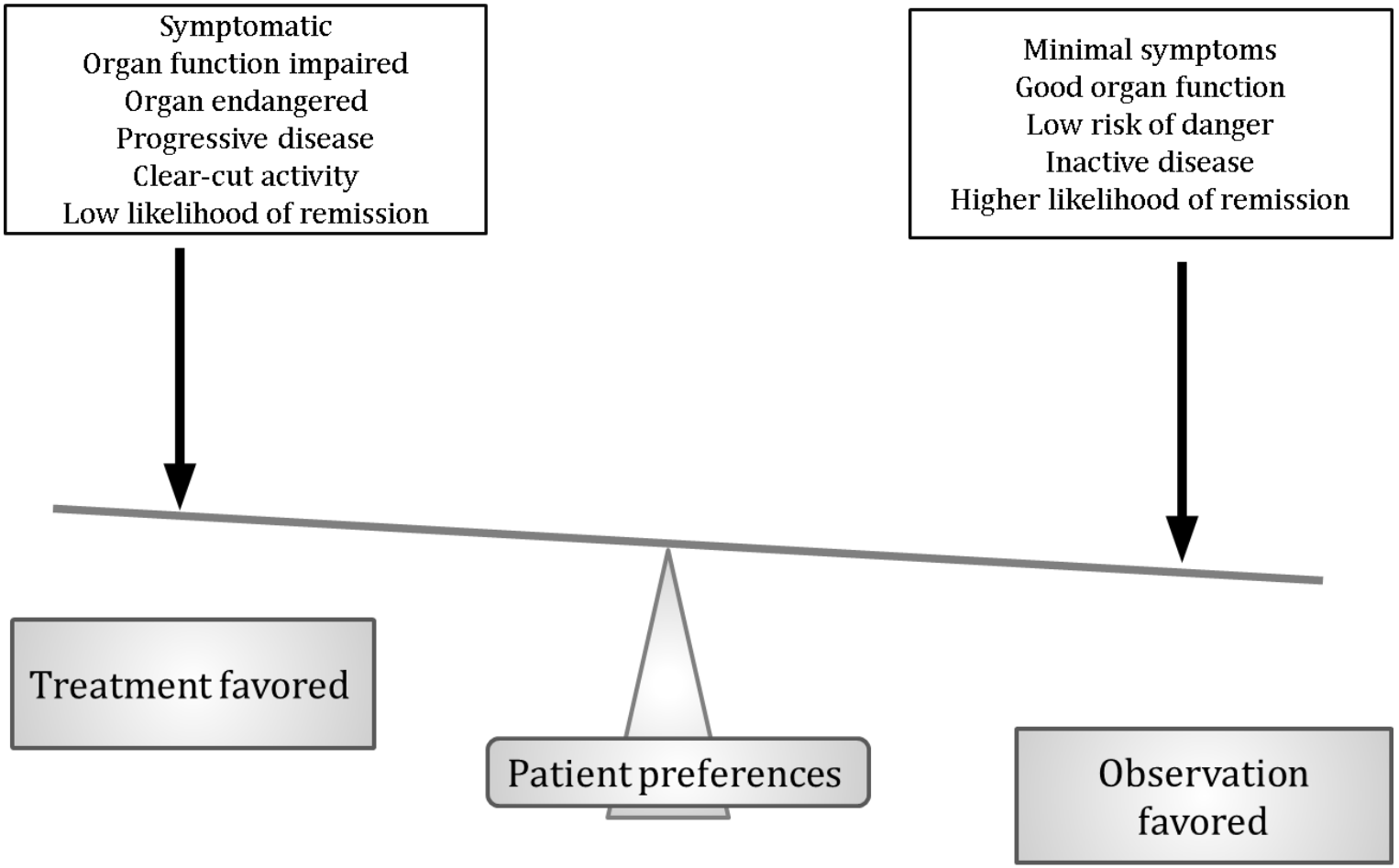


DE-MRI/PET Fusion

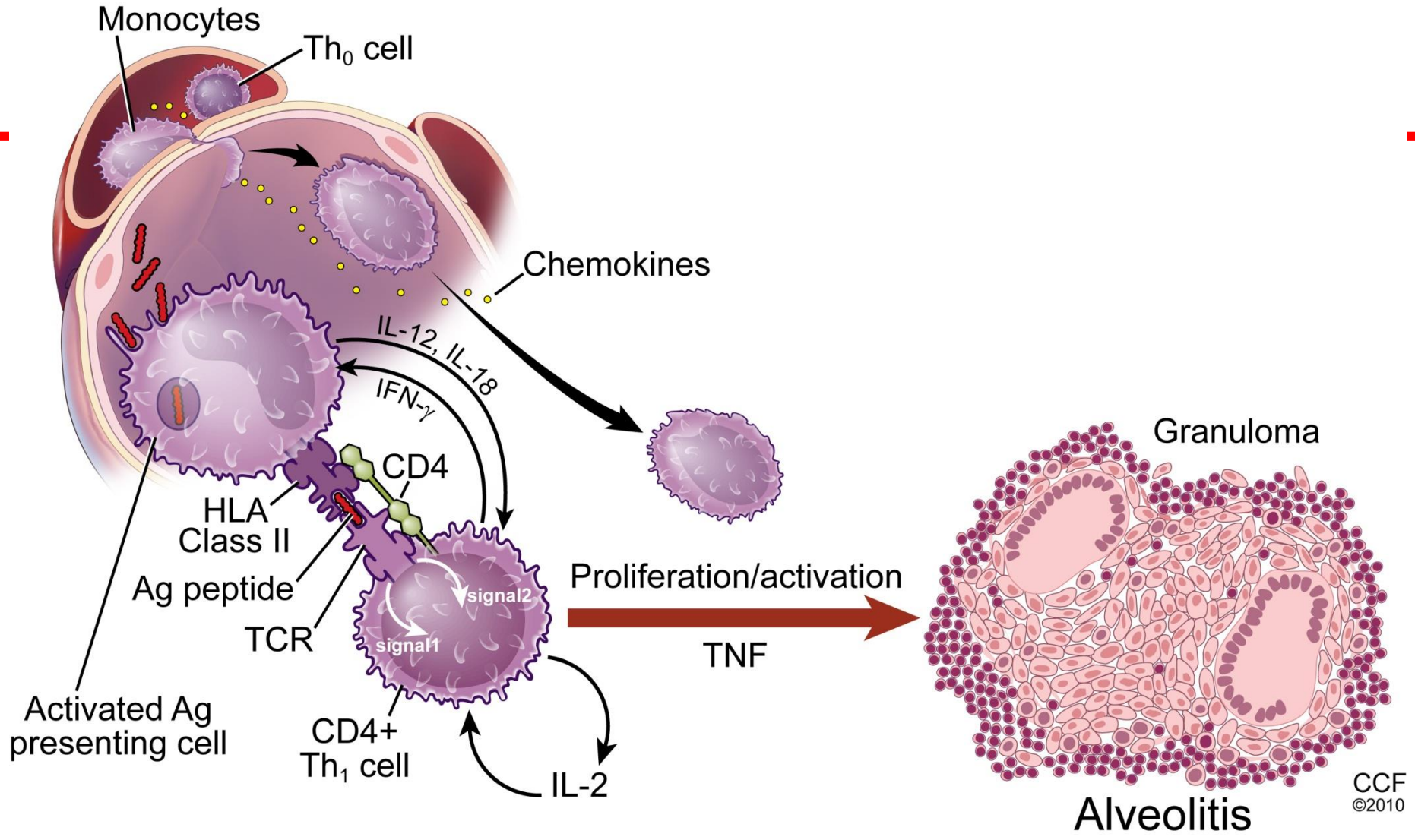
Sarcoidosis therapy: MICO

Masterful Inactivity with Cat-like Observation

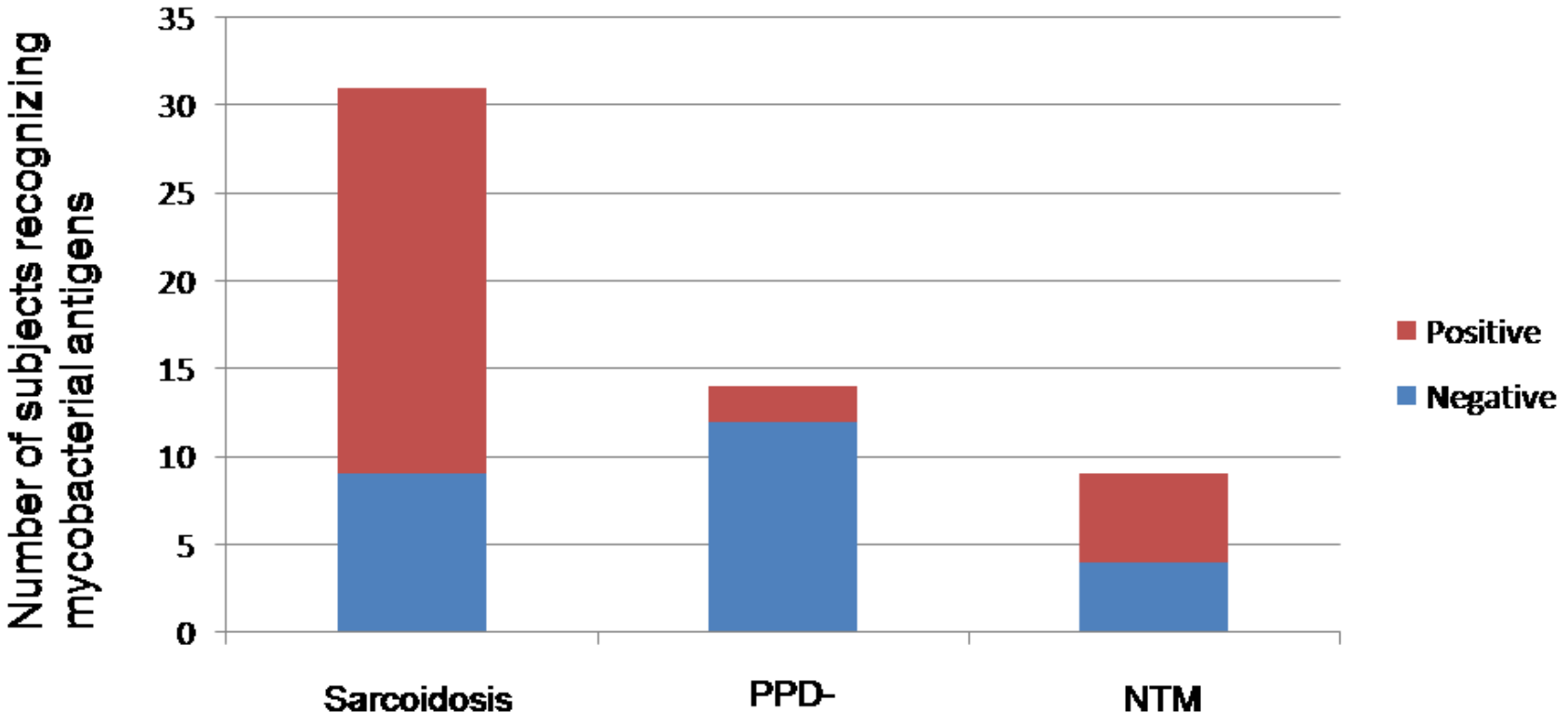
The decision to treat



Wijsenbeek MS. Clin Chest Med 2015

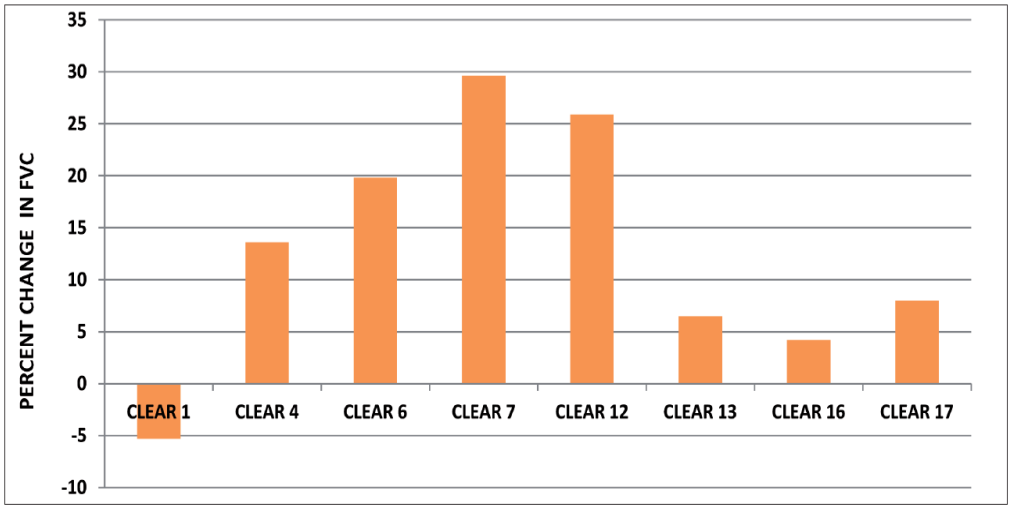

Monocytes
Th0 cell
Chemokines
IL-12, IL-18
IFN-γ
CD4
HLA
Class II
Ag peptide
TCR
signal2
signal1
Activated Ag
presenting cell
CD4+
Th1 cell
IL-2
Proliferation/activation
TNF
Granuloma
Alveolitis
CCF
©2010

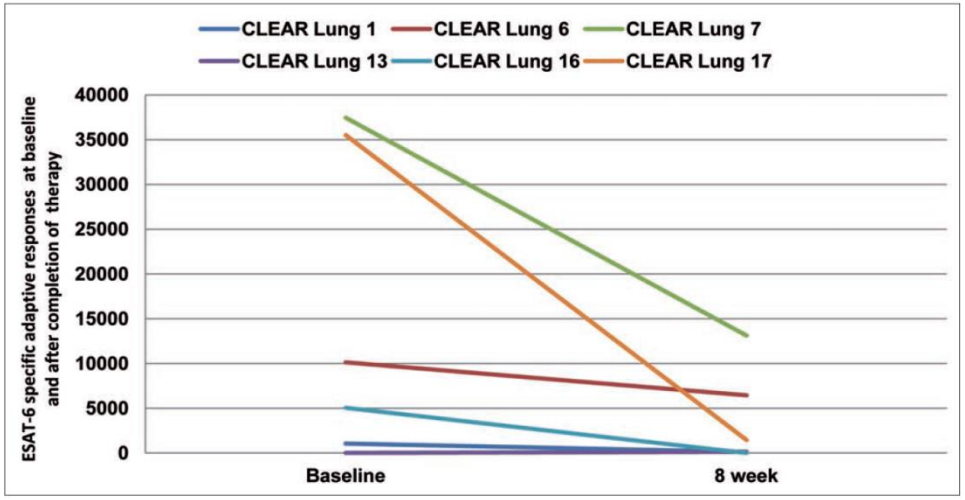
Sarcoidosis patients respond to multiple mycobacterial antigens



Oswald-Richter KA. Respir Res. *In press*

Effects of 8 weeks of CLEAR therapy in pulmonary sarcoidosis





Drake WP. SVDLD 2014

Major sarcoidosis trends

- Emerging diagnostic technology
  - FDG-PET
  - EBUS-TBNA
  - Cardiac sarcoidosis
- Move away from steroids
- Demographic shift
- Focus on non-inflammatory aspects
  - Pulmonary hypertension
  - Fatigue, neuropathy, comorbidities
- Collaboration

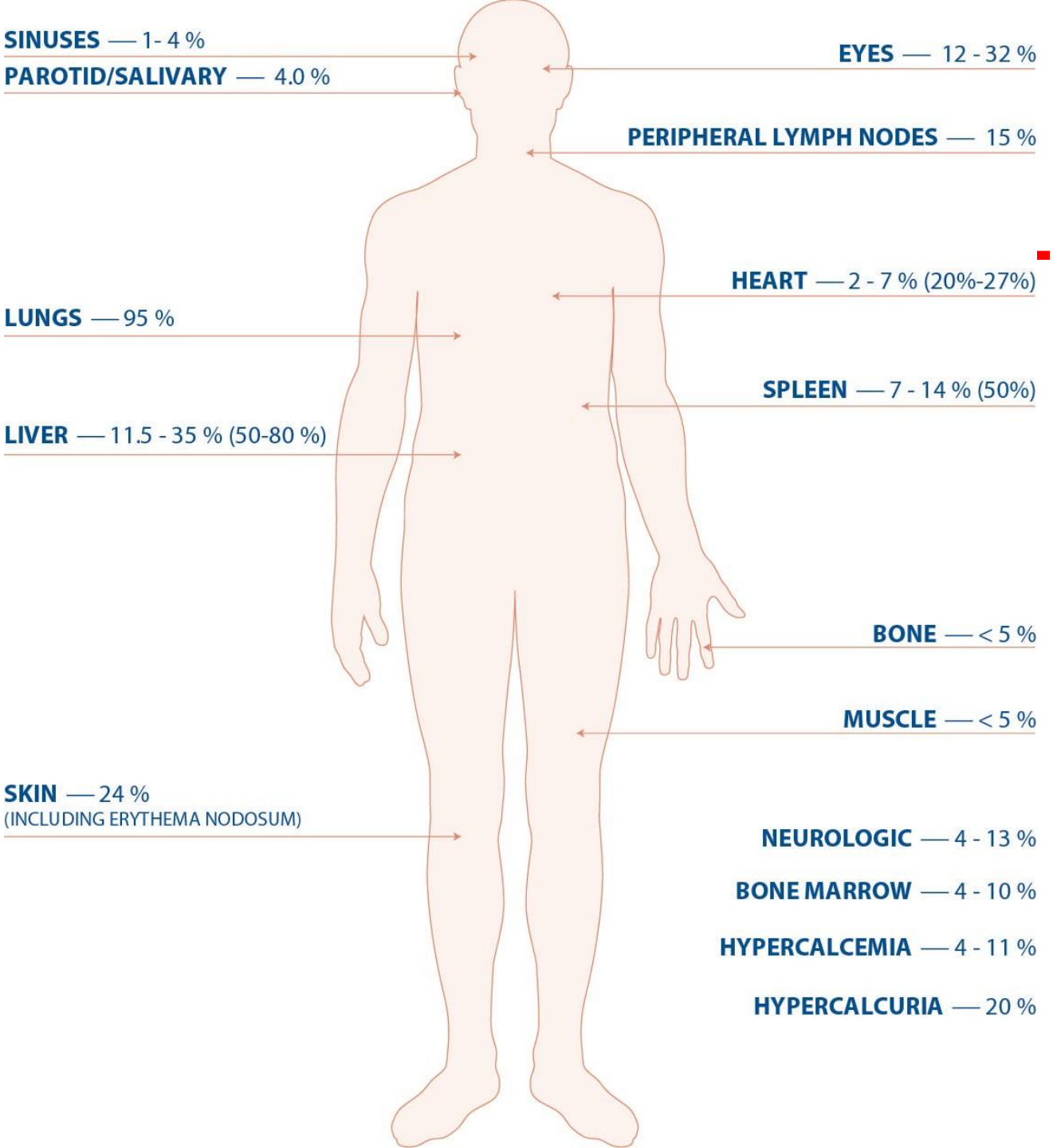
Conclusions

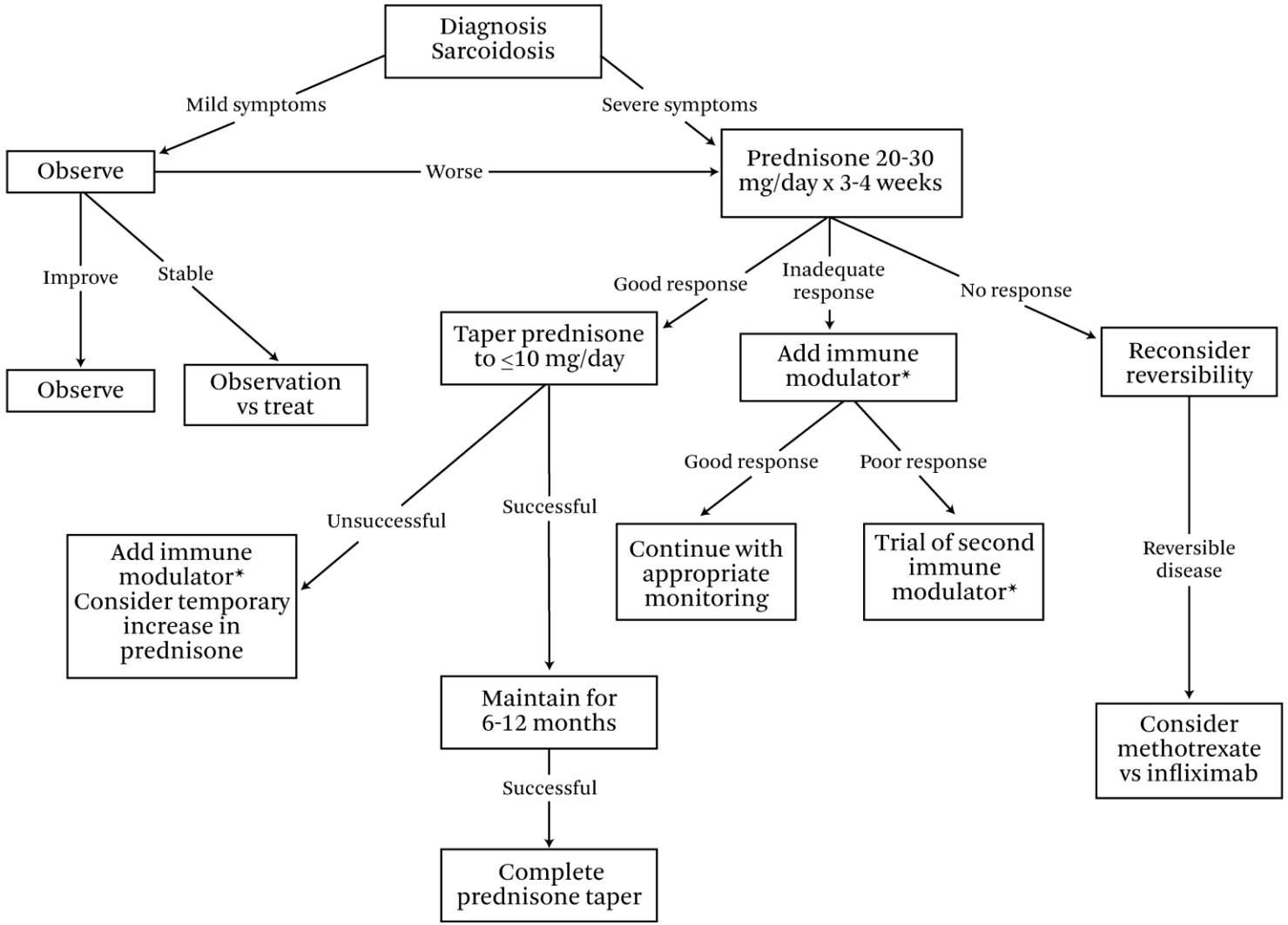
- Interstitial lung diseases ≈ 200 types
- History, exam, PFTs and radiology diagnose most ILDs
- PFTs are crucial for assessment and longitudinal care
- UIP ≠ IPF
- Pulmonary fibrosis ≠ IPF

Sarcoidosis misconceptions

- Affects younger adults
- Cardiac disease is rare
- Usefulness of ACE level
- Most commonly treated with prednisone

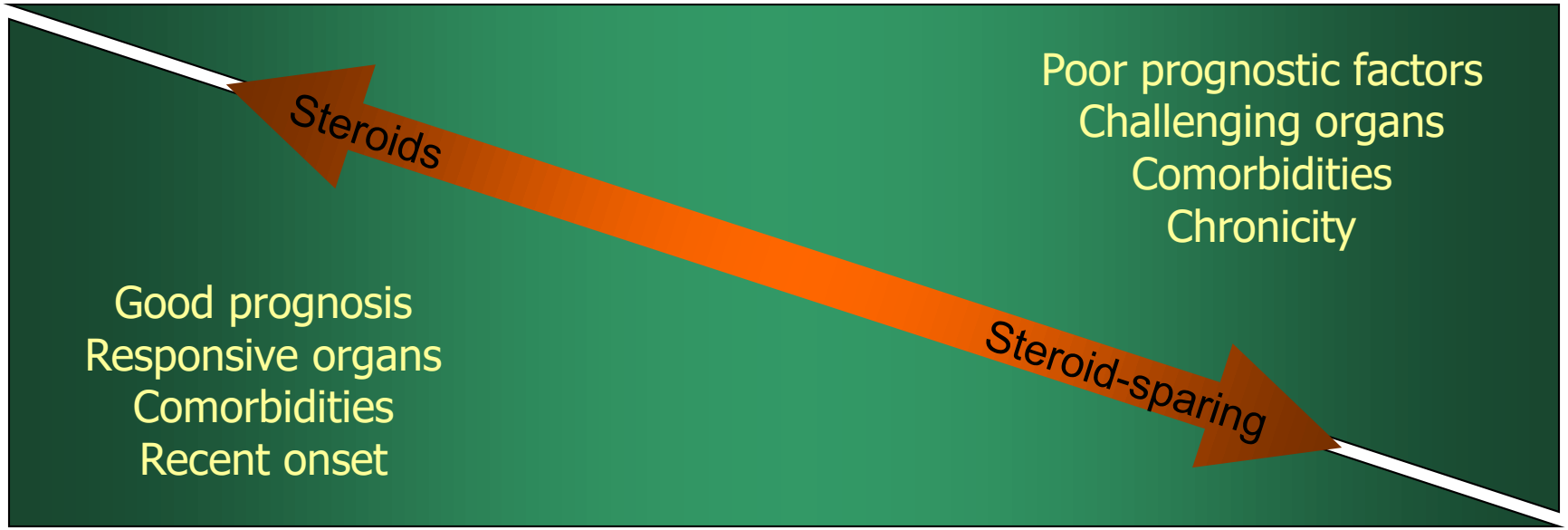
THANK YOU FOR THE INVITATION!


SINUSES — 1- 4 %
PAROTID/SALIVARY — 4.0 %
EYES — 12 - 32 %
PERIPHERAL LYMPH NODES — 15 %
HEART — 2 - 7 % (20%-27%)
LUNGS — 95 %
SPLEEN — 7 - 14 % (50%)
LIVER — 11.5 - 35 % (50-80 %)
BONE — < 5 %
MUSCLE — < 5 %
SKIN — 24 %
(INCLUDING ERYTHEMA NODOSUM)
NEUROLOGIC — 4 - 13 %
BONE MARROW — 4 - 10 %
HYPERCALCEMIA — 4 - 11 %
HYPERCALCURIA — 20 %

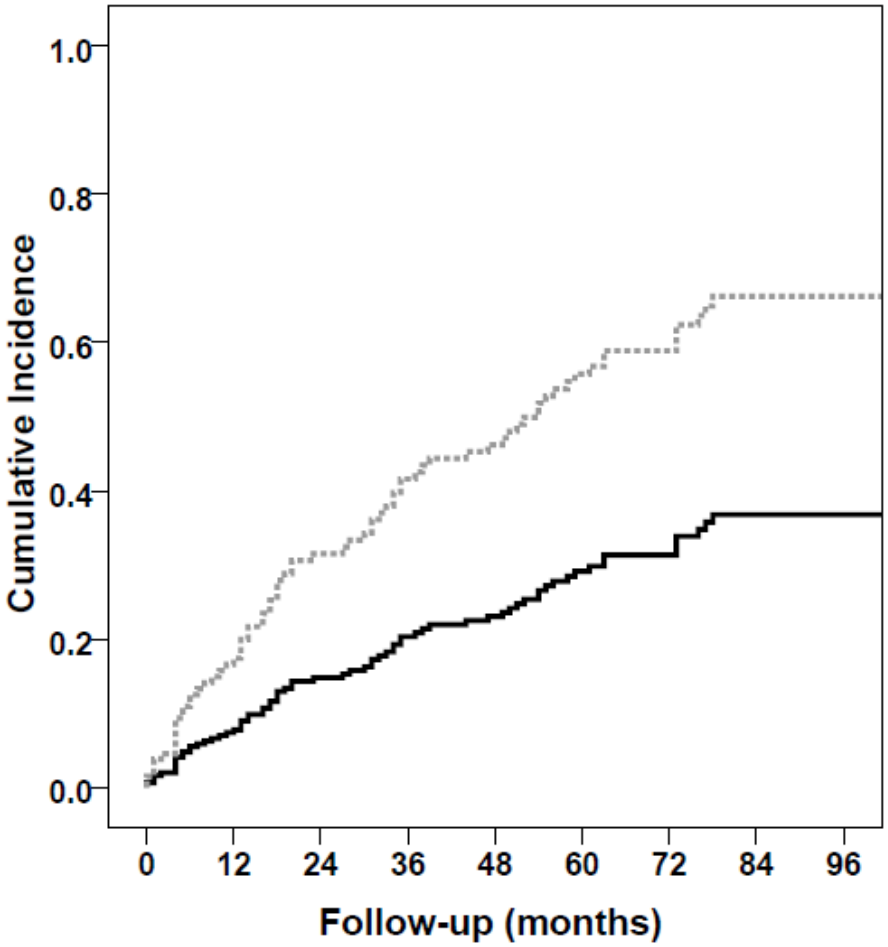


*Current options include - methotrexate, azathioprine, leflunomide, and mycophenolate.

One size does not fit all



Cumulative risk of steroid complications

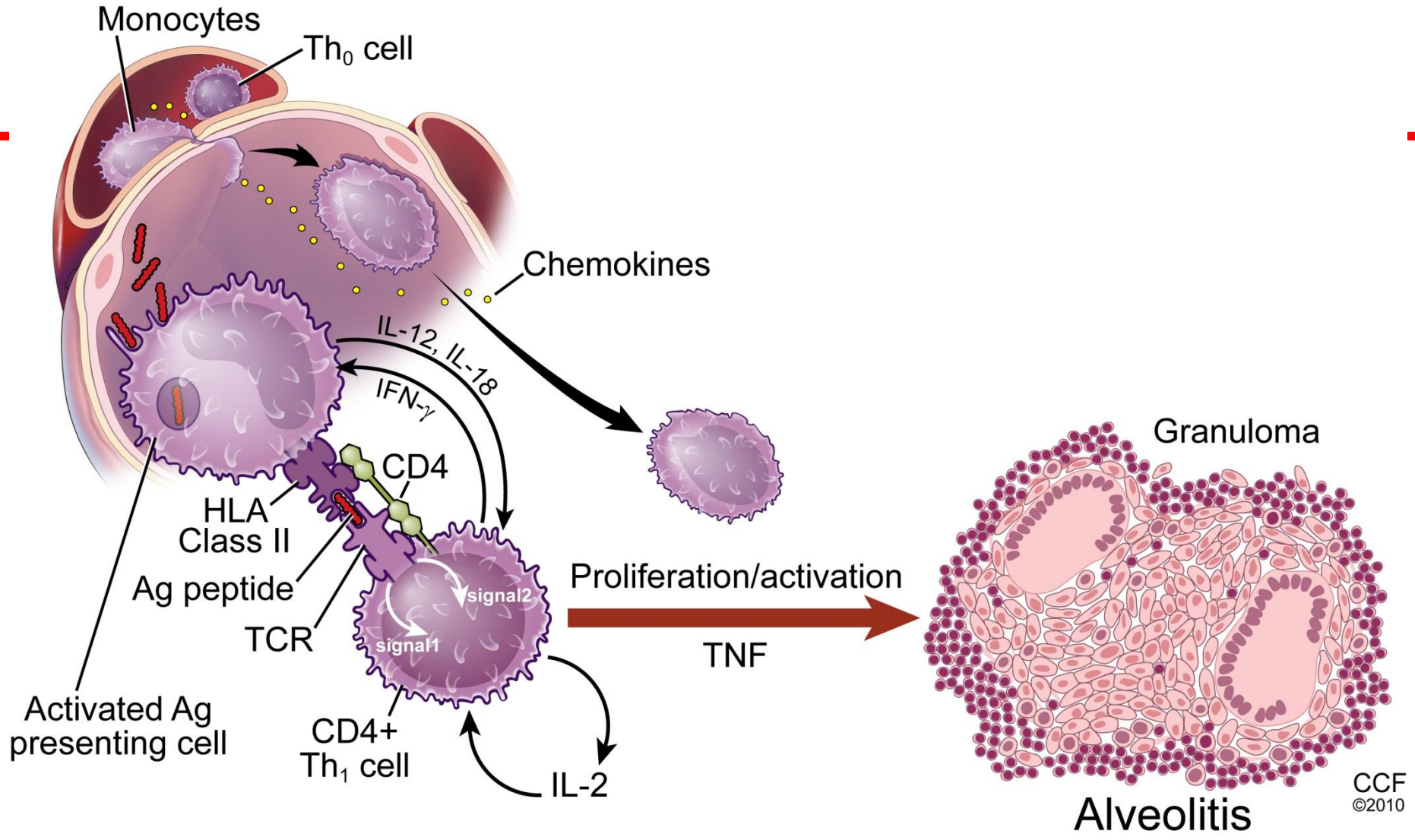


Hazard ratio: 2.37 (1.34-4.17)

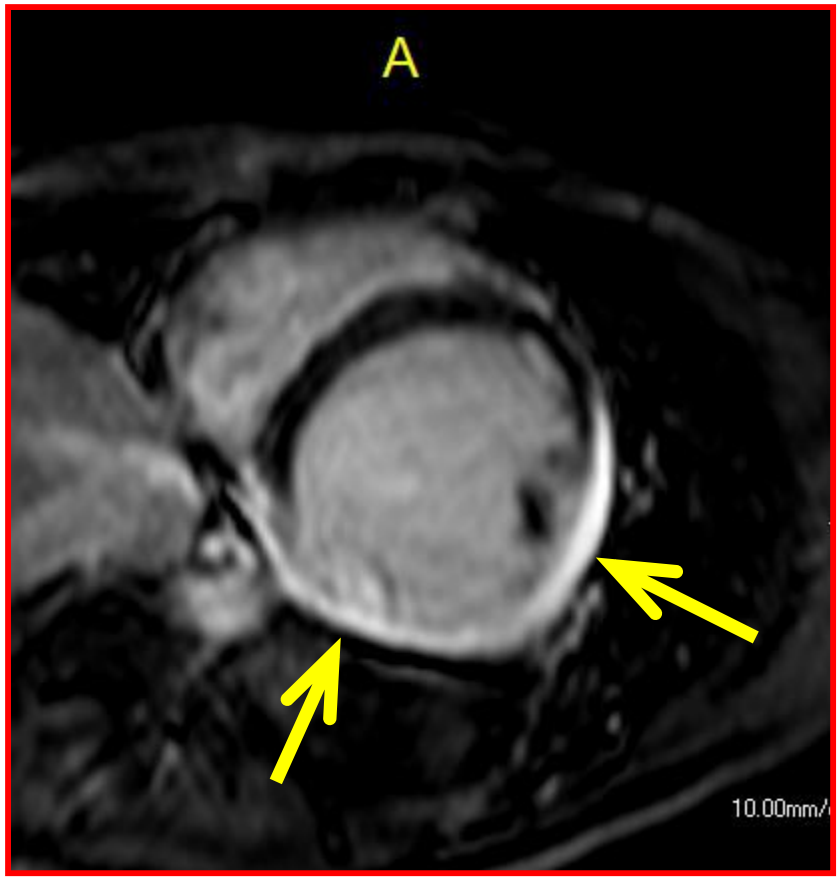
Other covariates

Age/yr	1.021	(1.001-1.041)
Pre-existing disease	2.27	(1.33-3.89)

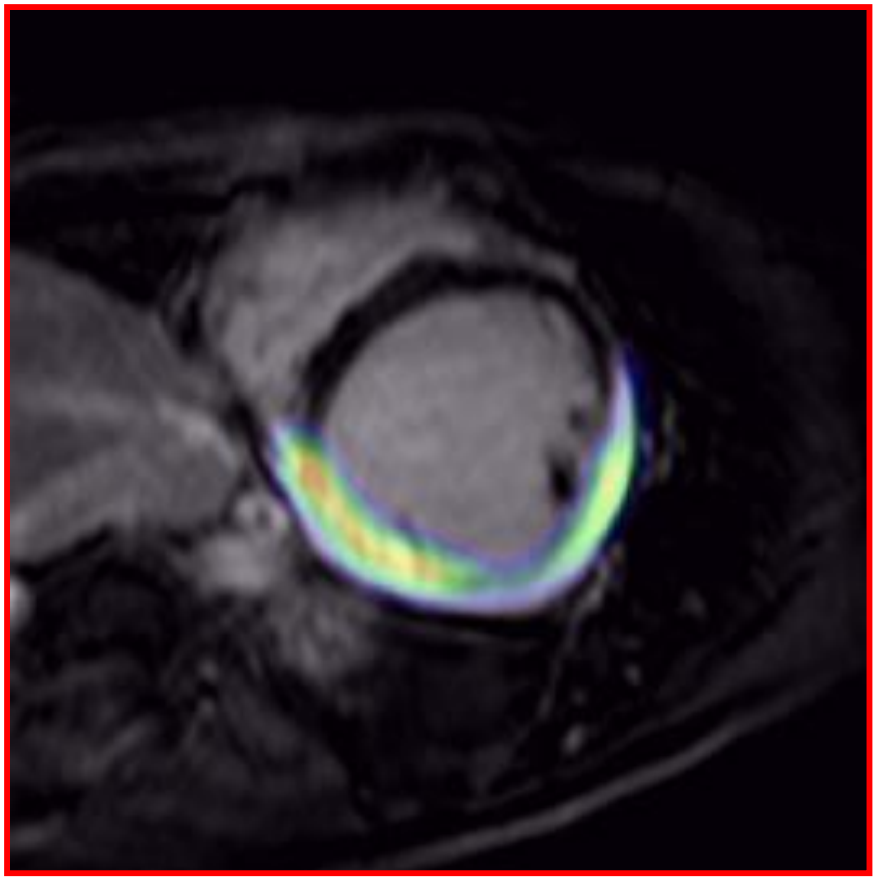
Duration of steroids (mos)	1.023	(1.013-1.033)
Cumulative dose (grams)	1.038	(1.019-1.056)


Monocytes
Th0 cell
Chemokines
IL-12, IL-18
IFN-γ
CD4
HLA
Class II
Ag peptide
TCR
signal2
signal1
Activated Ag
presenting cell
CD4+
Th1 cell
IL-2
Proliferation/activation
TNF
Granuloma
Alveolitis
CCF
©2010

Concordance

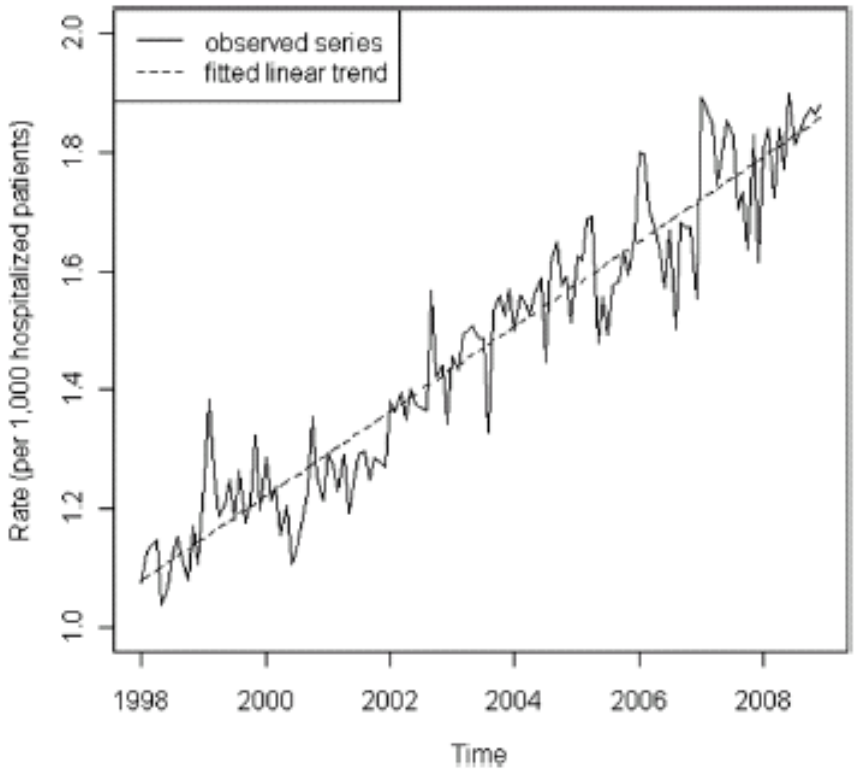


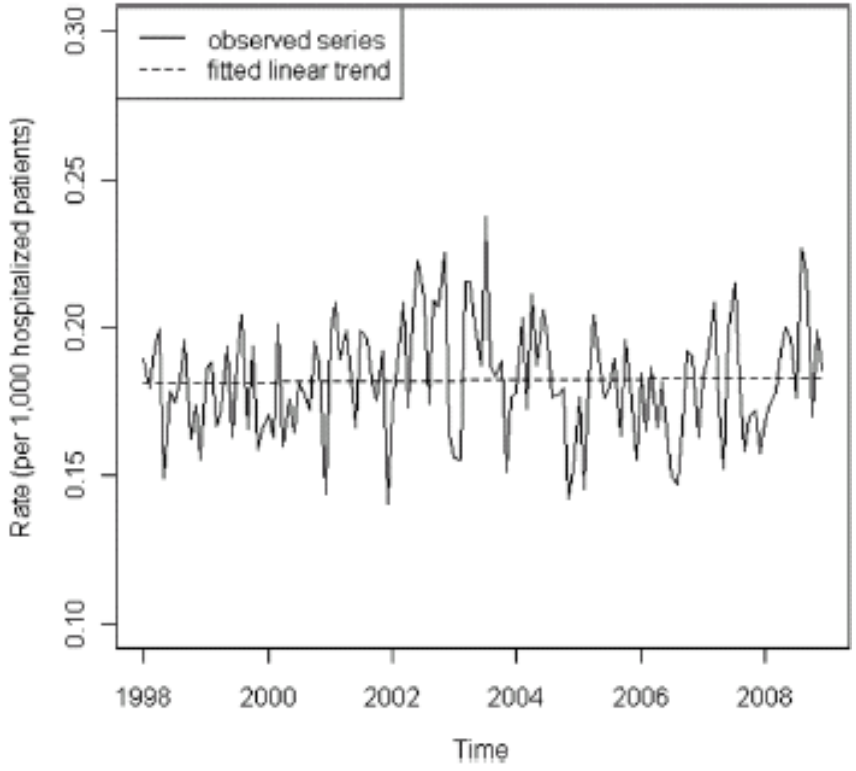
DE-MRI



DE-MRI/PET Fusion

Rising number of sarcoidosis hospitalizations in the US





Gerke AK. BMC Pulm Med 2012

Clinical outcome after 5 years

Clinical outcome score	Therapy	No (%)
Resolved	Never	59 (12%)
Resolved	Not within 1 year	44 (9%)
Minimal (<25% of peak disease)	Never	47 (9%)
Minimal (<25% of peak disease)	Not within 1 year	38 (8%)
Persistent, no current therapy	Never	41 (8%)
Persistent, no current therapy	Not within 1 year	54 (11%)
Current therapy, asymptomatic		57 (11%)
Current therapy, symptomatic		115 (23%)
Current therapy, worsening		45 (9%)

32%

Baughman RP. Sarcoidosis Vasc Diffuse Lung Dis 2011

Prognosis versus clinical features

Characteristics Associated with Worse Prognosis
Age > 40 at onset
African American
Requirement for steroids
Extrapulmonary involvement Cardiac Neurologic (except isolated CN palsy) Lupus pernio Splenomegaly Hypercalcemia Osseous disease
Pulmonary Involvement Stage 3-4 chest radiograph Pulmonary hypertension Significant lung function impairment Moderate to severe dyspnea on presentation BAL neutrophilia at presentation

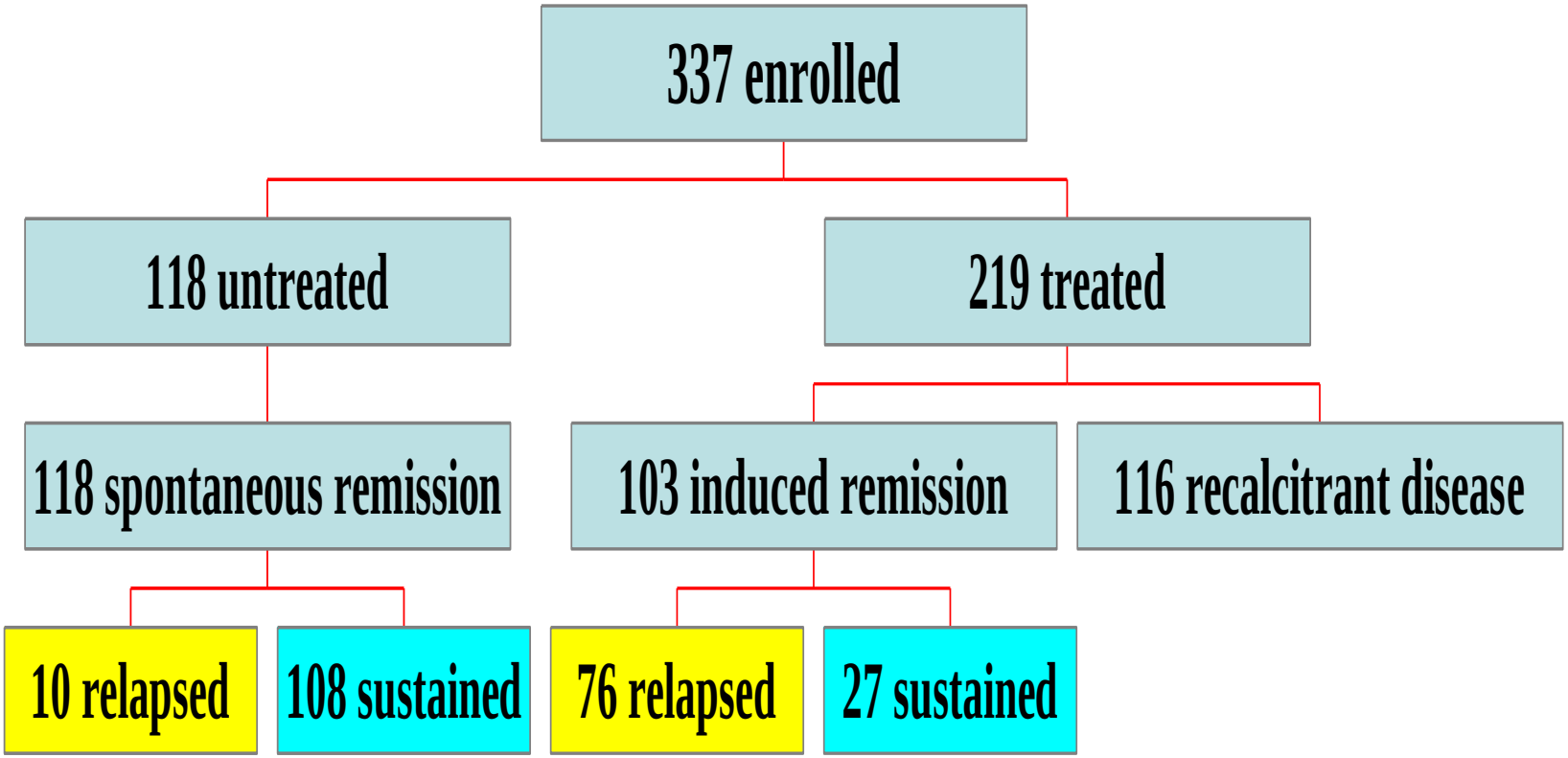
Effect of prolonged corticosteroids

Effects of 2 years steroid treatment in Stage 2/3 patients

	FVC		DLCO	
	CS	Placebo	CS	Placebo
Unchanged	11 (37%)	8 (40%)	9 (36%)	6 (37%)
Improved	13 (43%)	6 (30%)	13 (52%)	7 (44%)
Worsened	6 (20%)	6 (30%)	3 (12%)	3 (19%)
Total	30	20	25	16

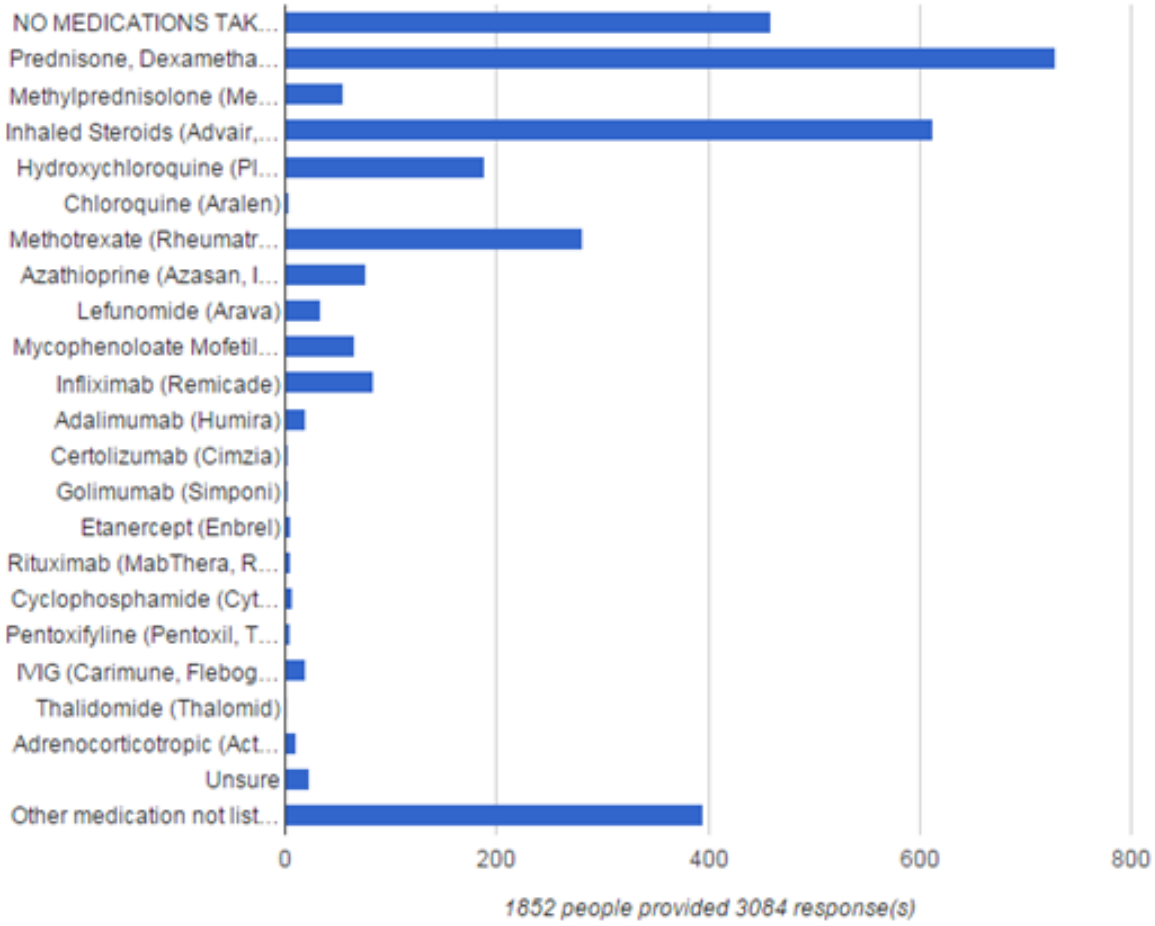
Zaki MH. NY State J Med 1987

Treated patients typically require ongoing treatment



Gottlieb JE. Chest 1997

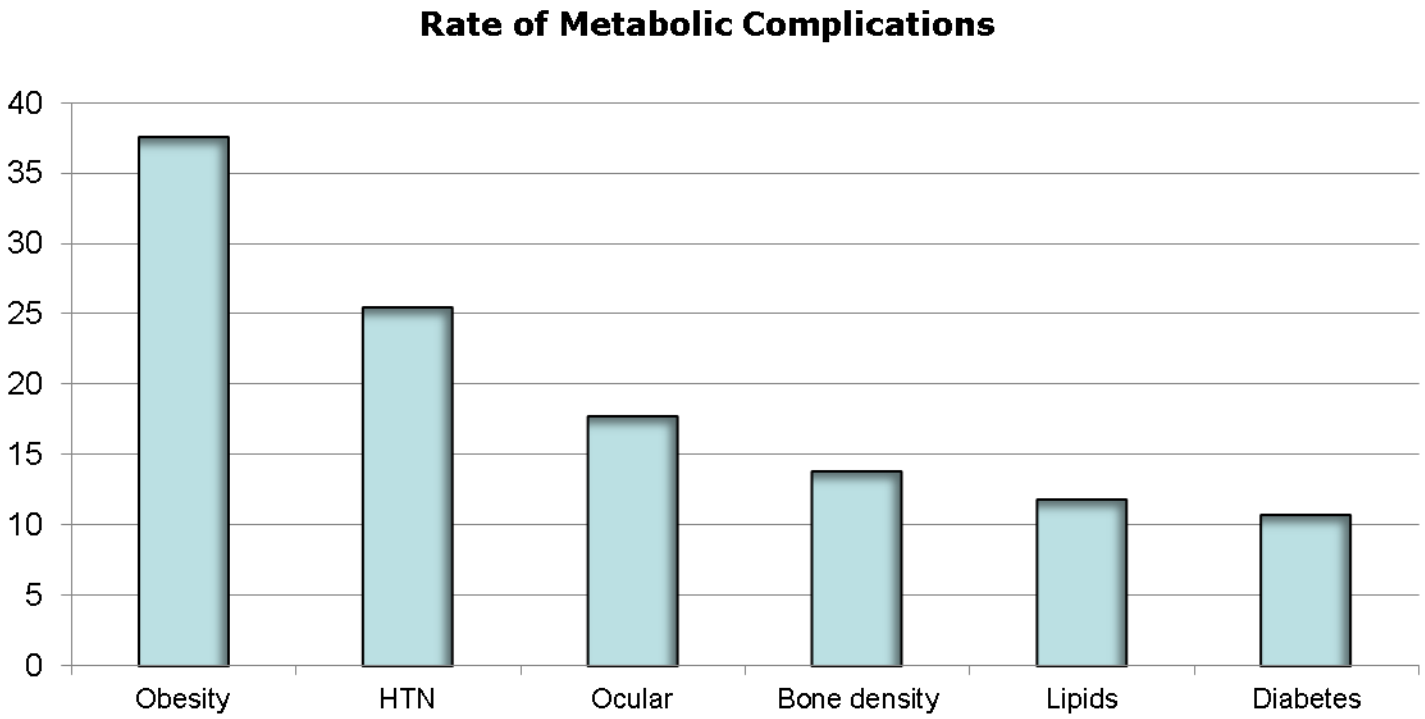
Medications in FSR registry population



RESULTS: Metabolic Complications among 154 new sarcoidosis patients seen at CCF

76 patients developed or had worsening

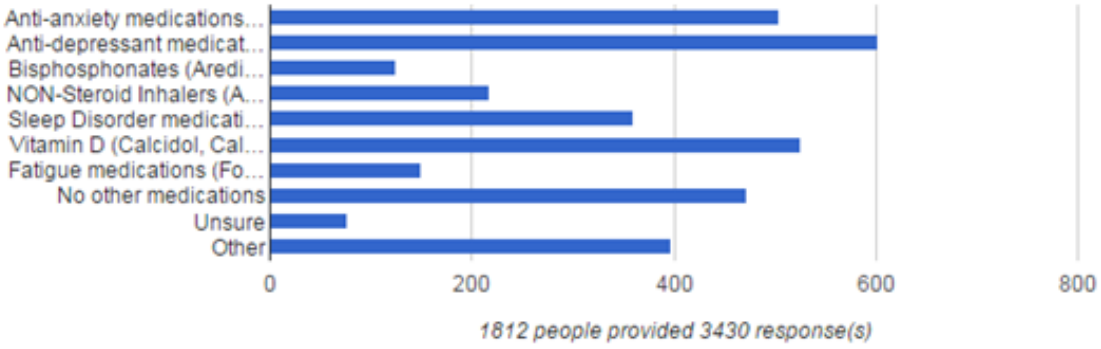
average of 1.9 ± 1 conditions per patient



Quality of life and use of steroids are opposite

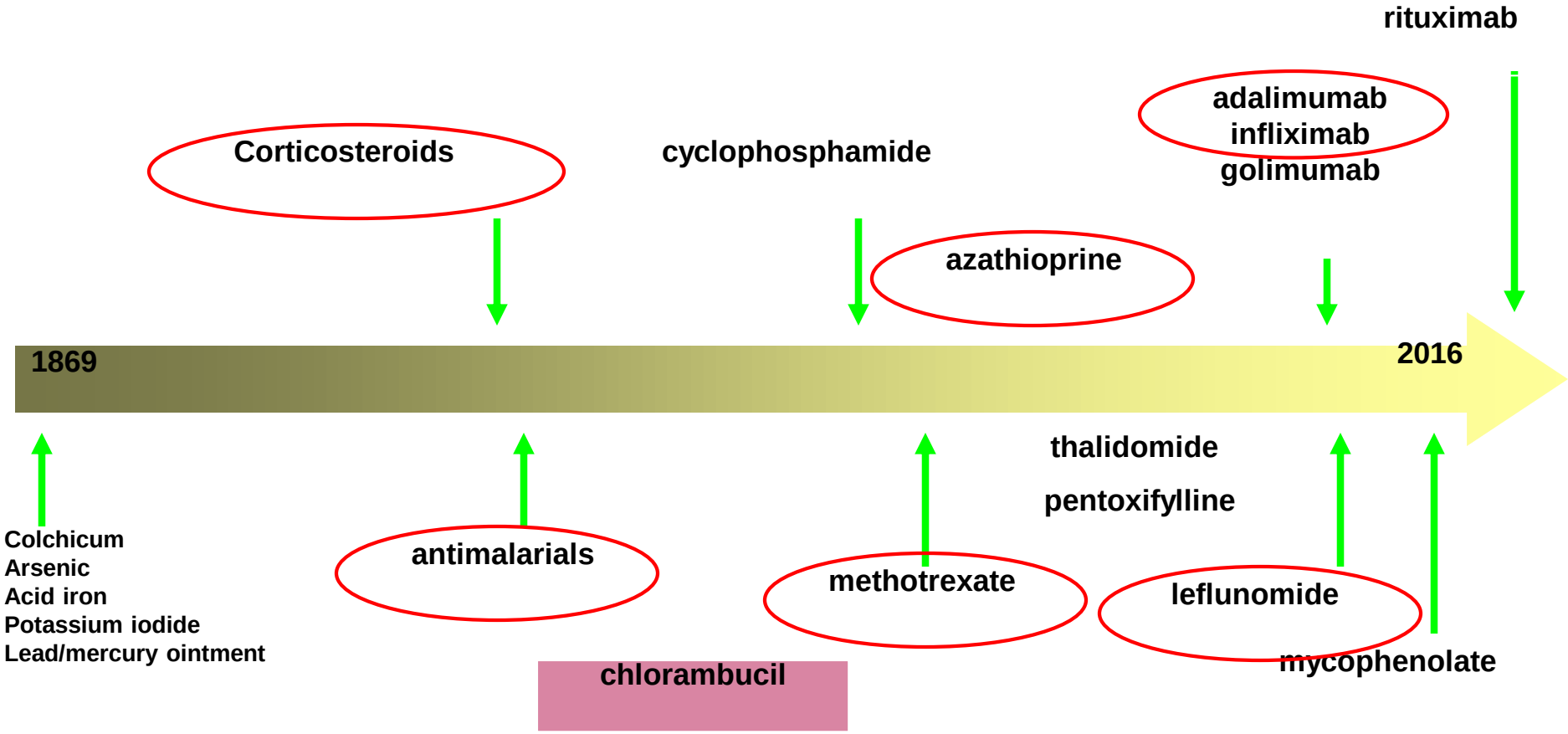
Table 3—*Differences in Predicted HRQL Scores Between Patient Groups Based on Oral Corticosteroid Treatment

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)					



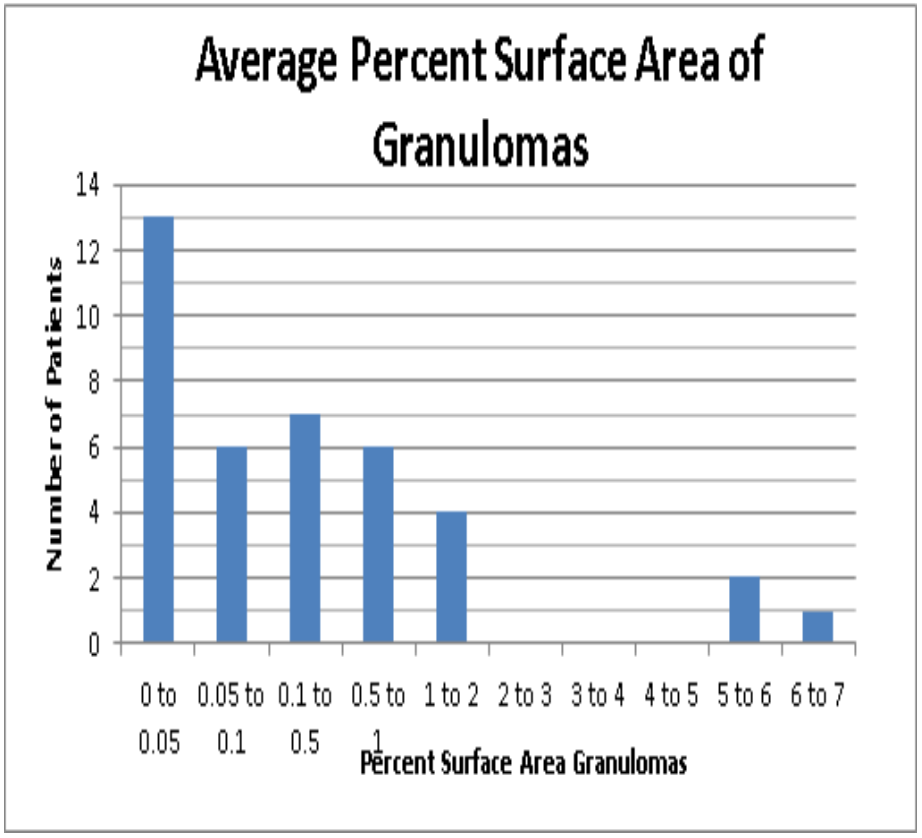
Cox CE. Chest 2004

Main immunosuppressive options

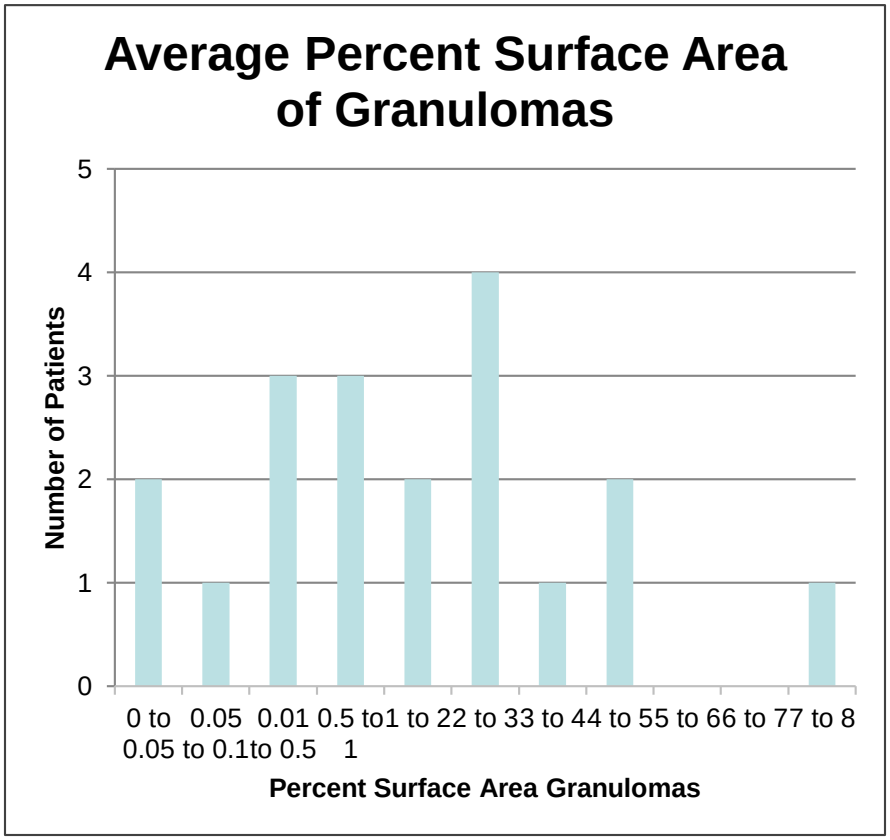


Explant granuloma burden

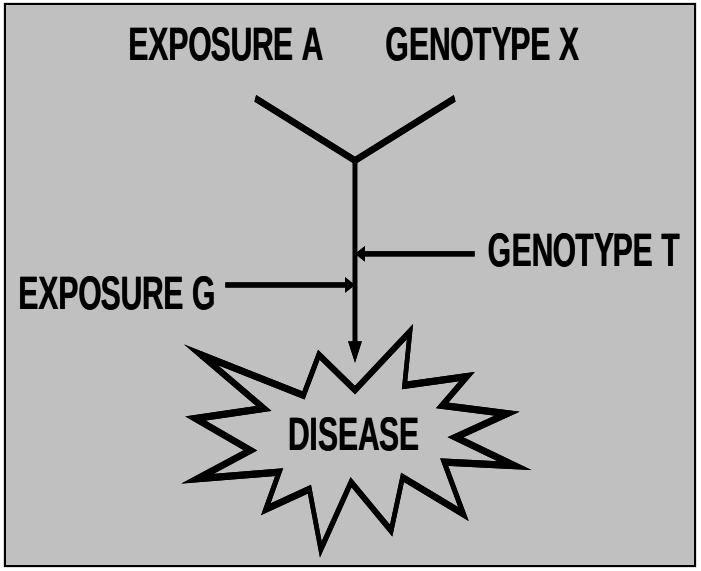
New diagnosis



Explant



Challenges for pathophysiologic research



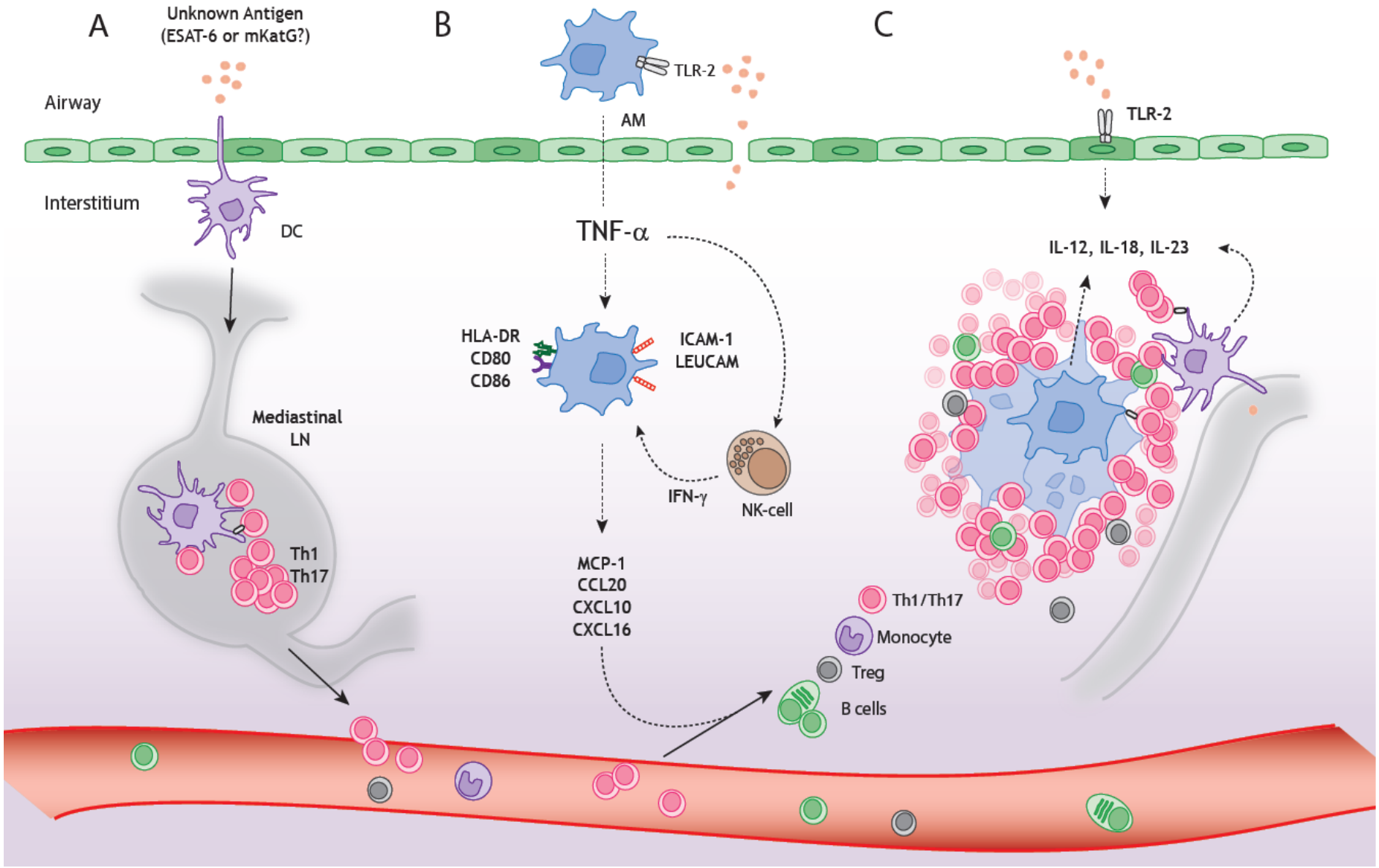
Sarcoidosis vs “sarcoidoses”

Genetic (? Etiologic) variability between populations

When is the disease studied?

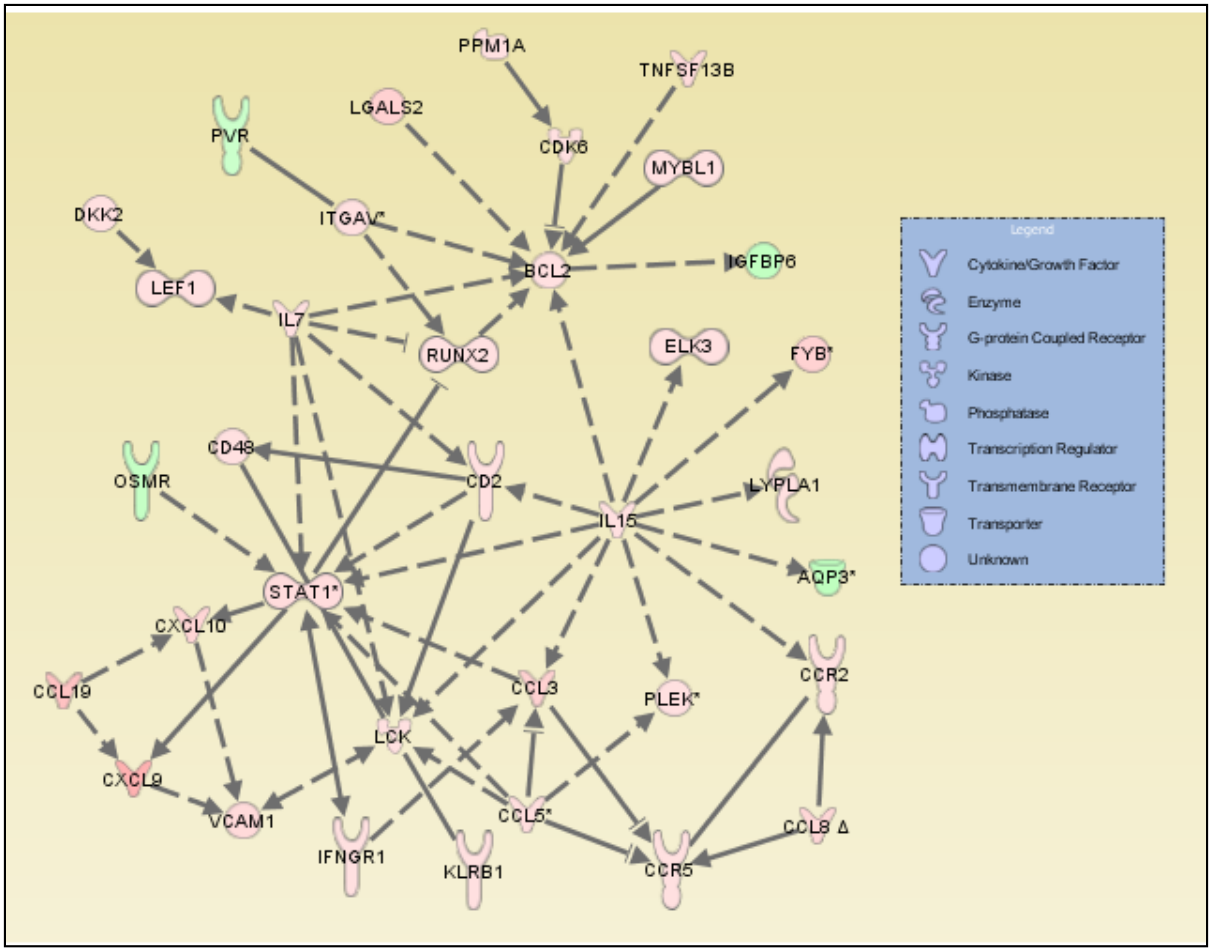
Where is the disease studied?

Absence of a robust animal model

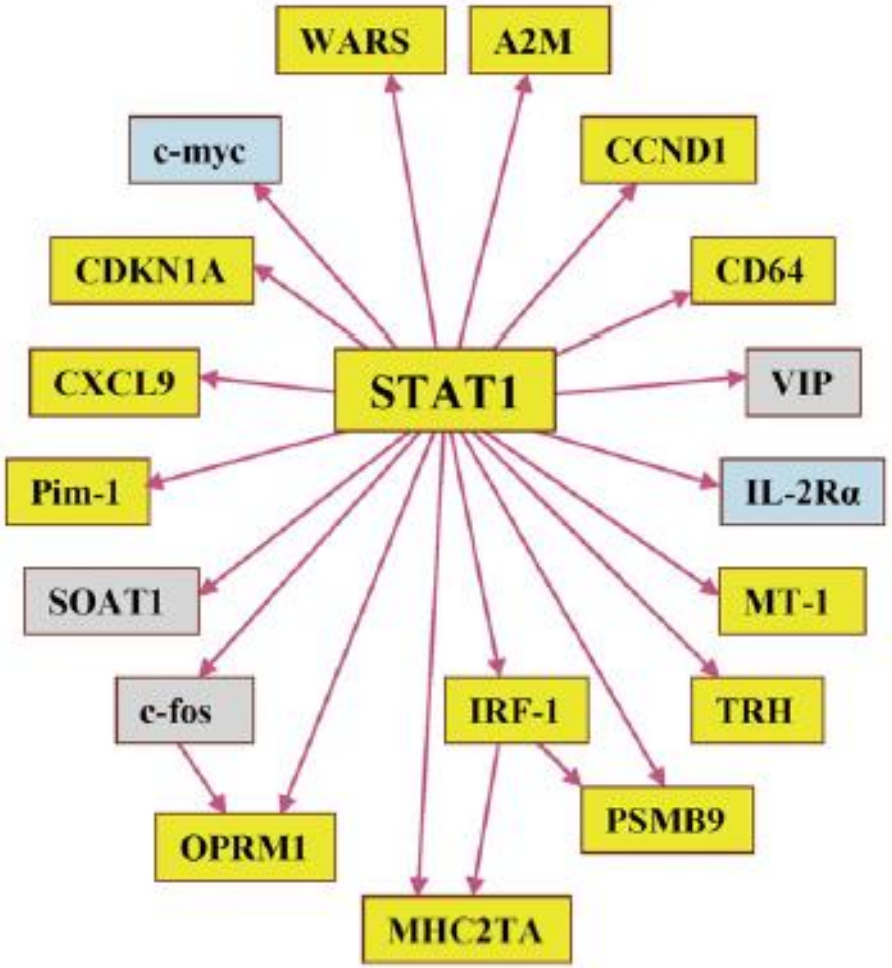


Broos CE. Front Immunol 2013

STAT1 plays a central role in sarcoidosis



Stat1-downstream genes in blood microarray

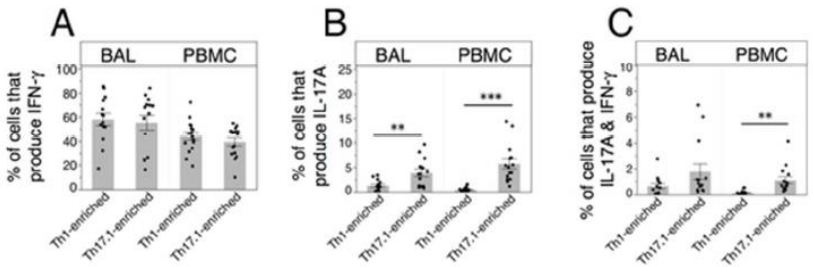


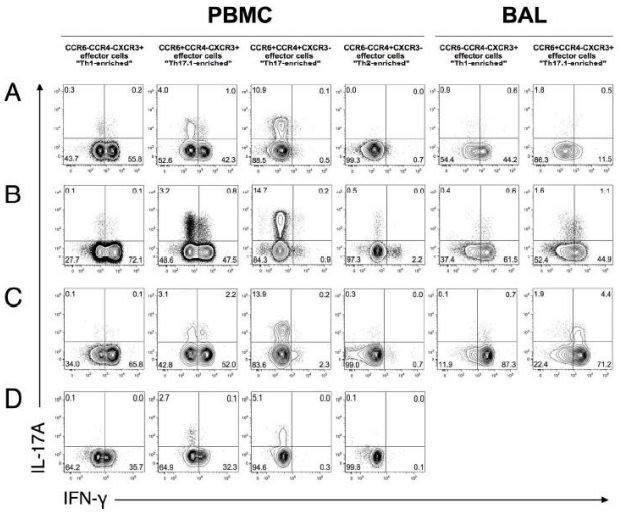
Rosenbaum JT. Clin Immunol 2009

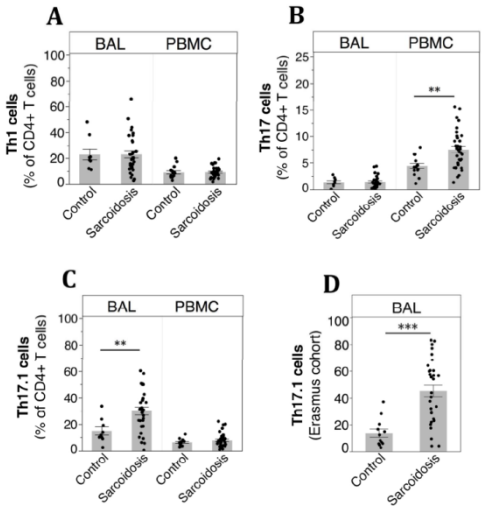
IFN-gamma producing Th17

Table 1: T effector cell subset phenotypes

	CCR4-/CXCR3+	CCR4+/CXCR3-
CCR6-	Th1	Th2
CCR6+	Th17.1	Th17

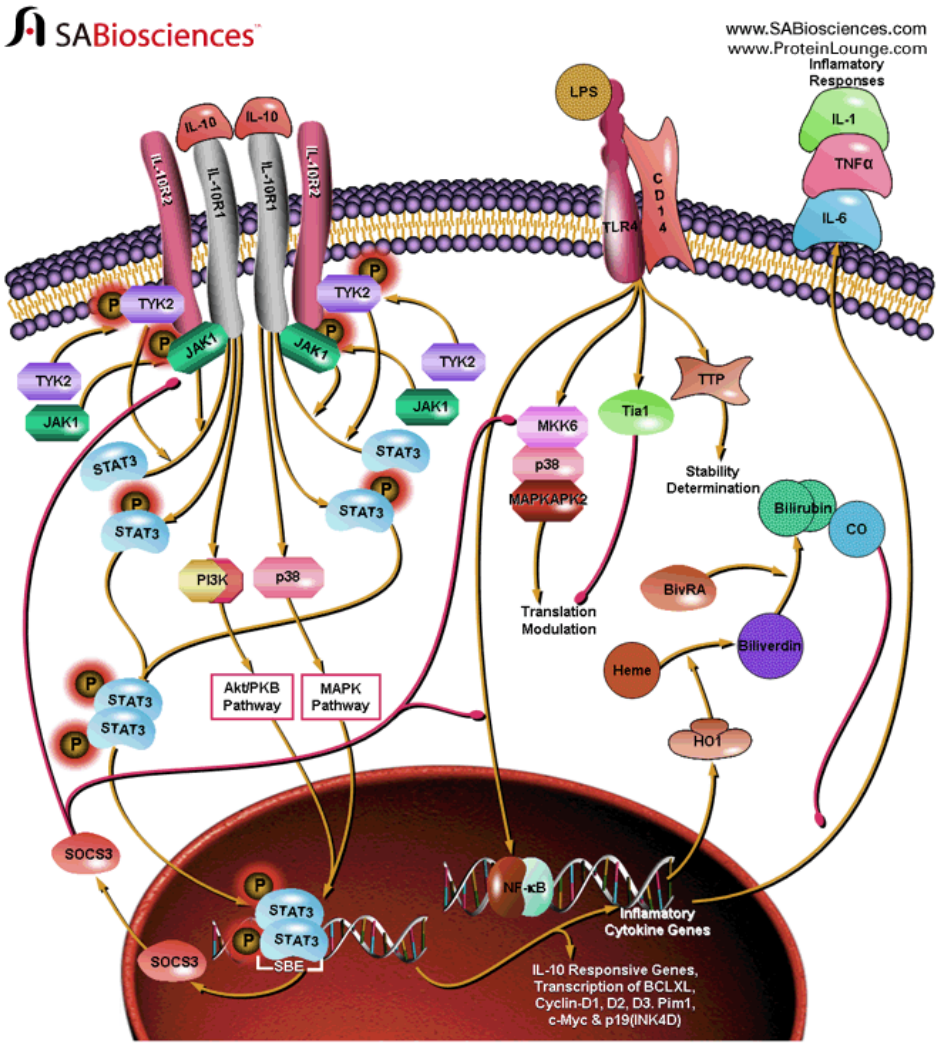


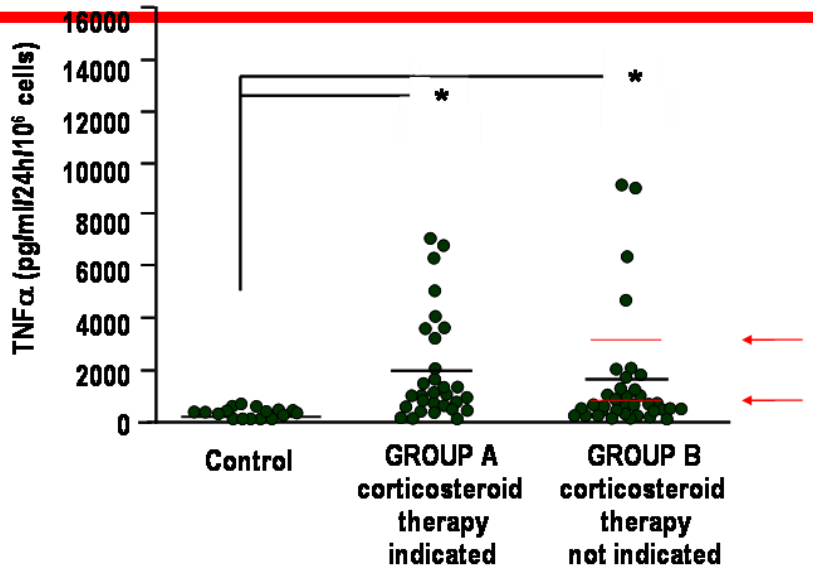


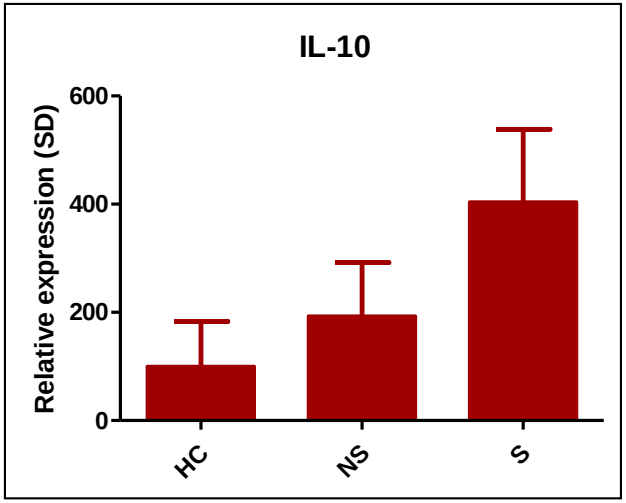


Ramstein J. AM J Respir Crit Care Med. In press.

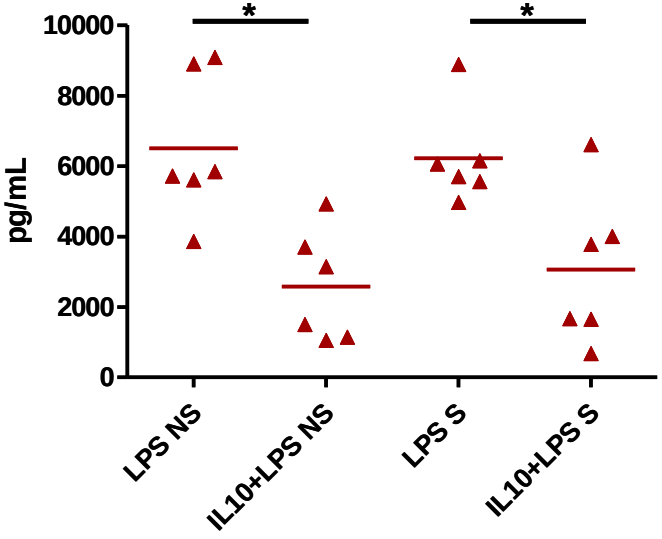
IL-10 antagonism of TNF

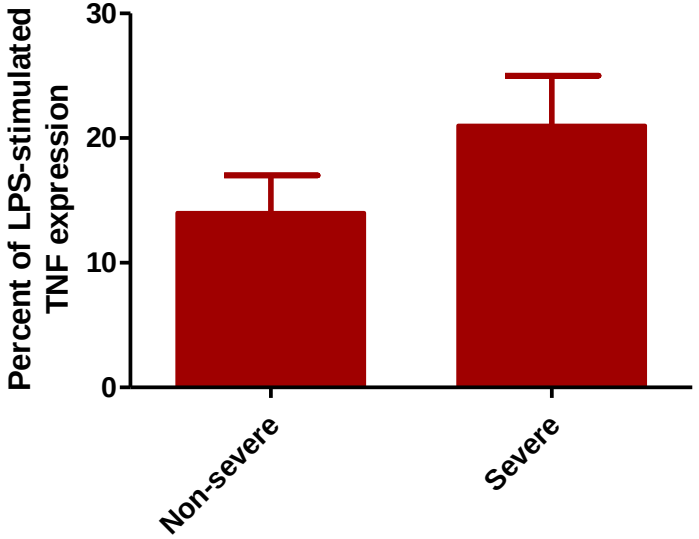




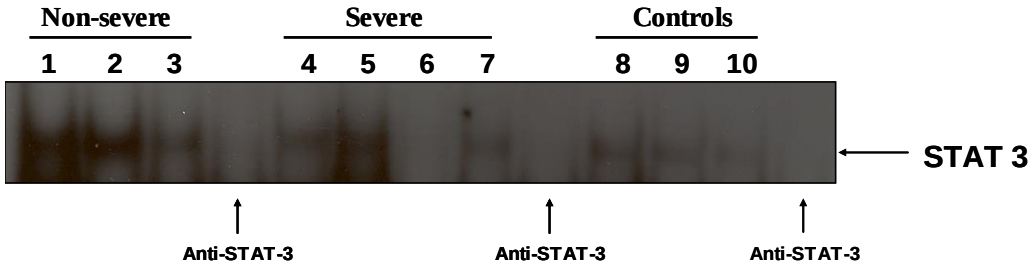


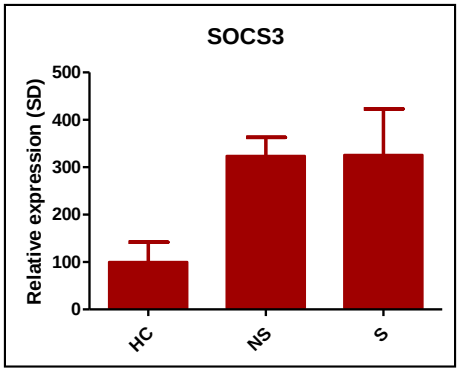
Treatment-requiring patients versus STAT3

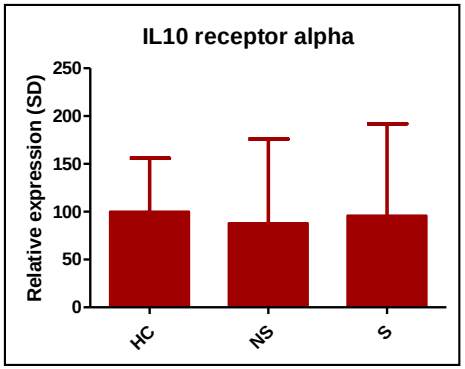


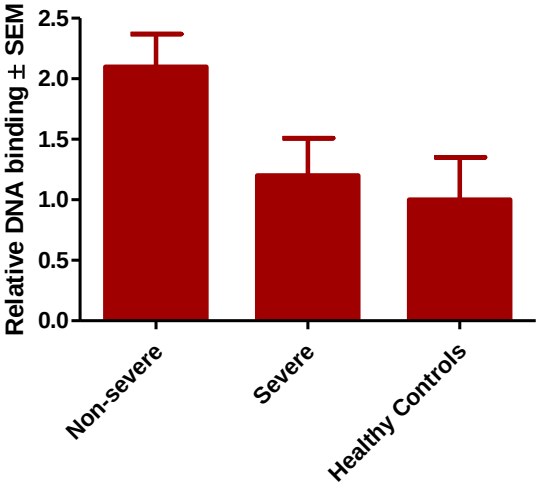


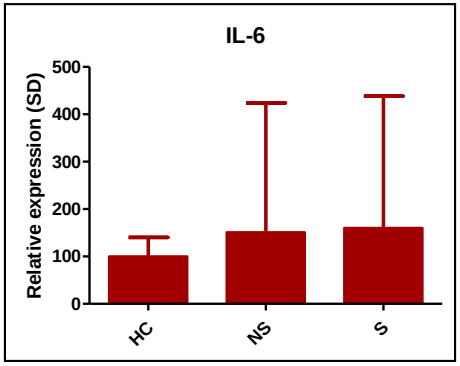
Enhanced STAT3 phosphorylation in resolving sarcoidosis

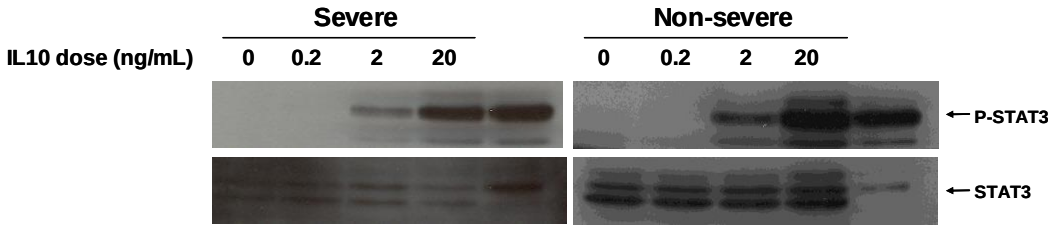




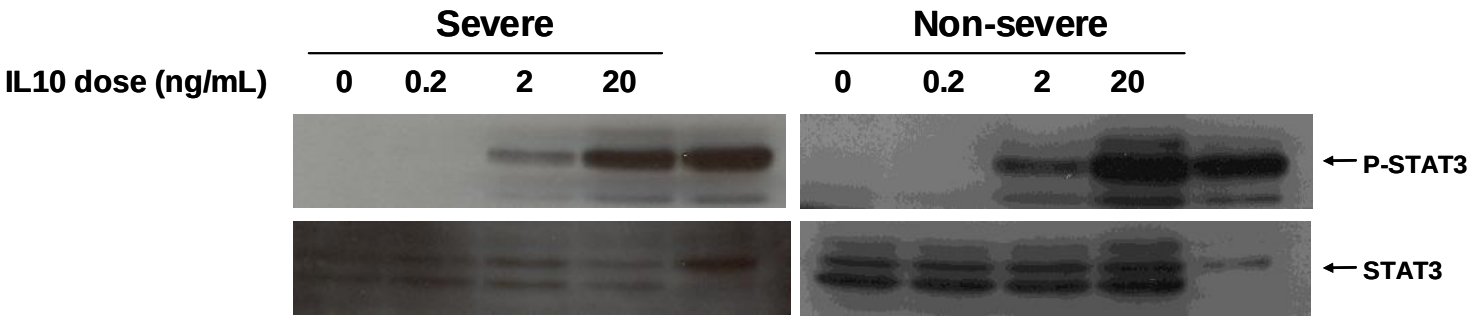


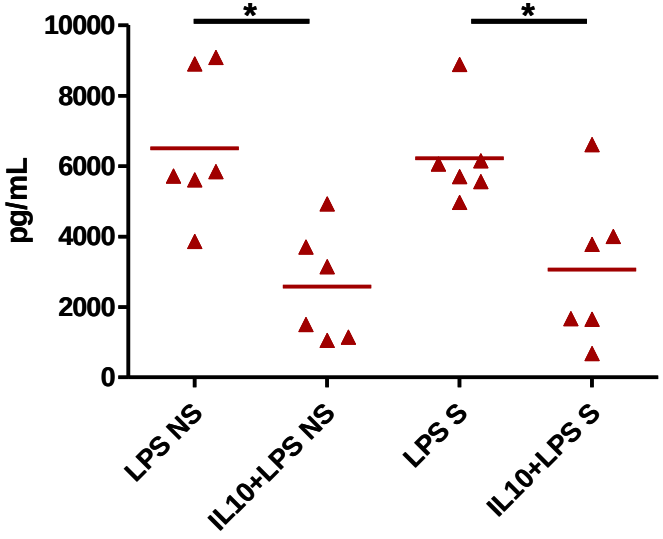


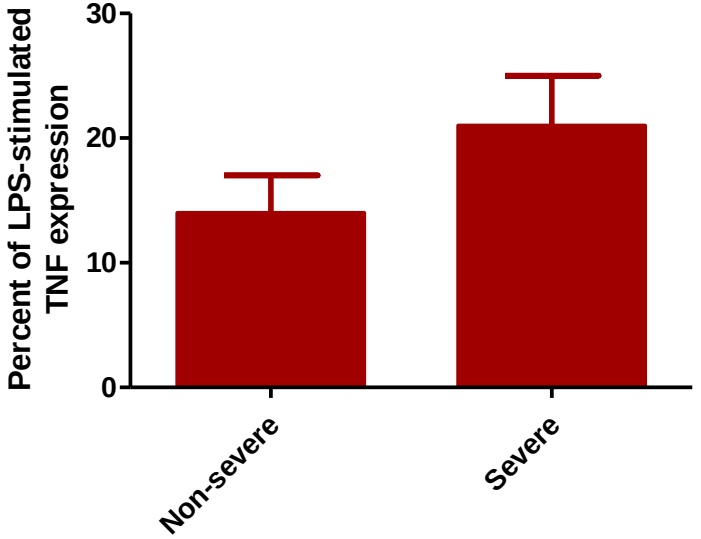




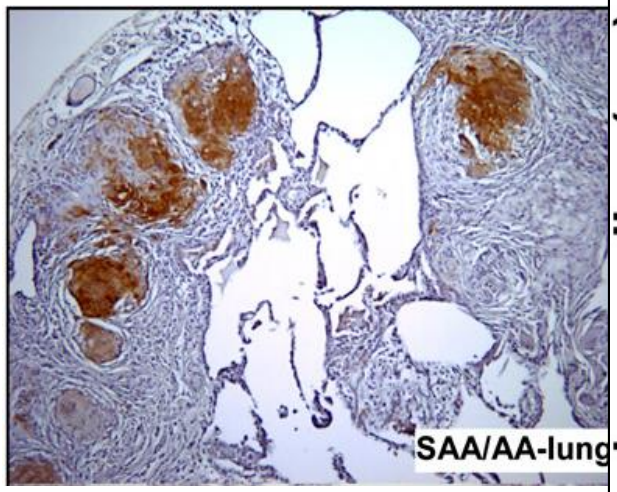
Treatment-requiring patients versus STAT3

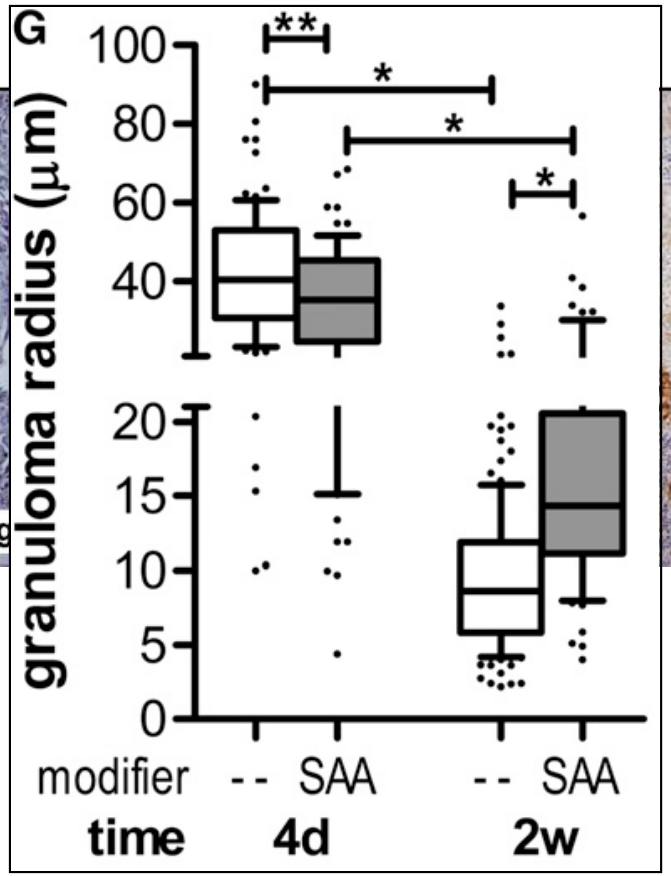


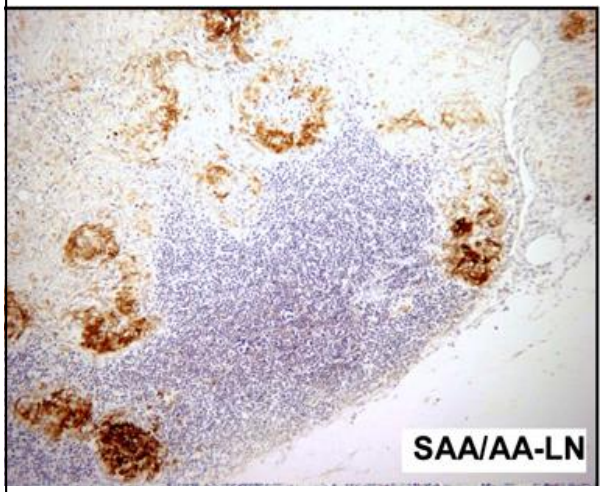




Physicochemical similarity of the Kveim reagent and amyloid protein



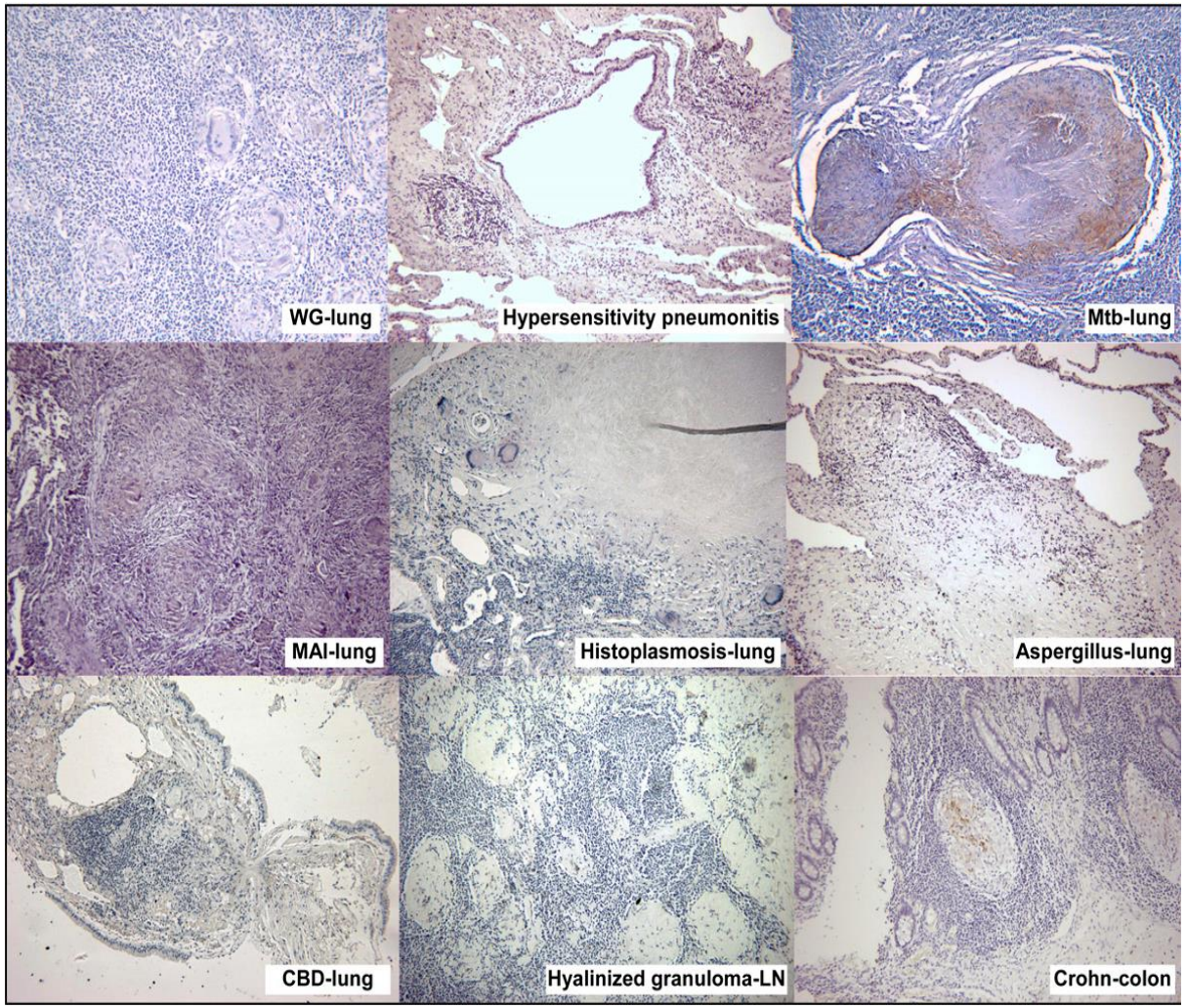




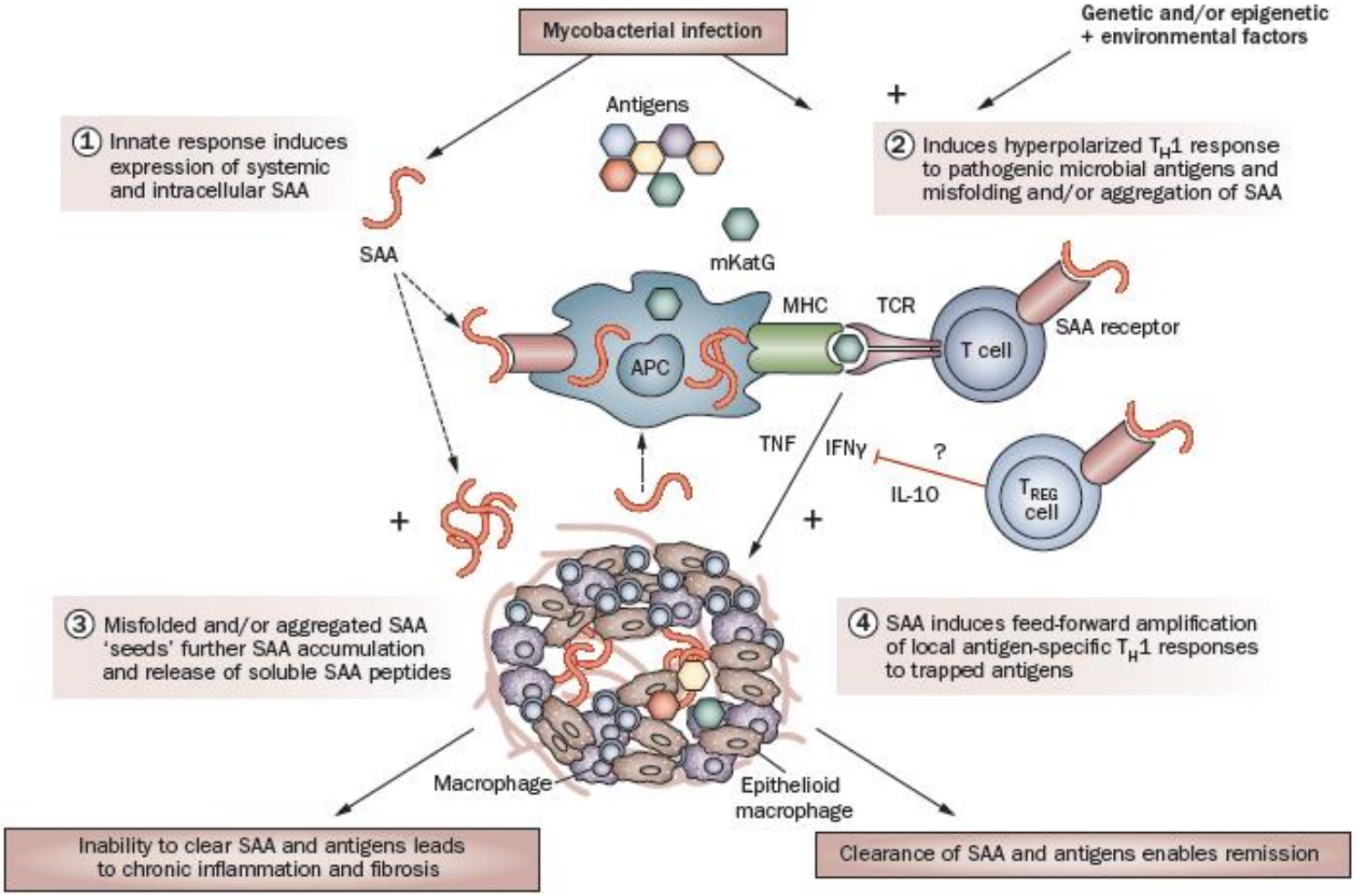
katG rat granuloma model

Chen ES. Am J Respir Crit Care Med 2010

Amyloid A staining in non-sarcoidosis granulomas

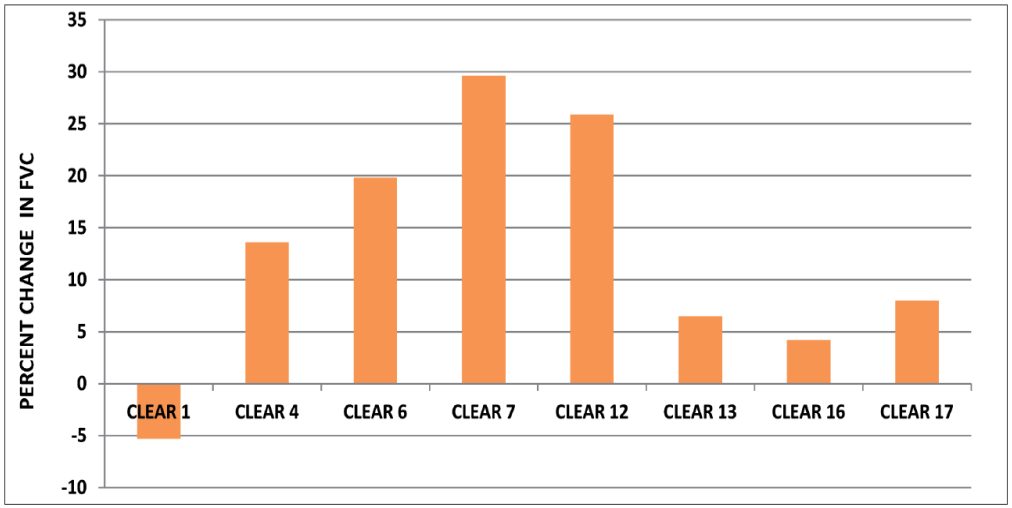


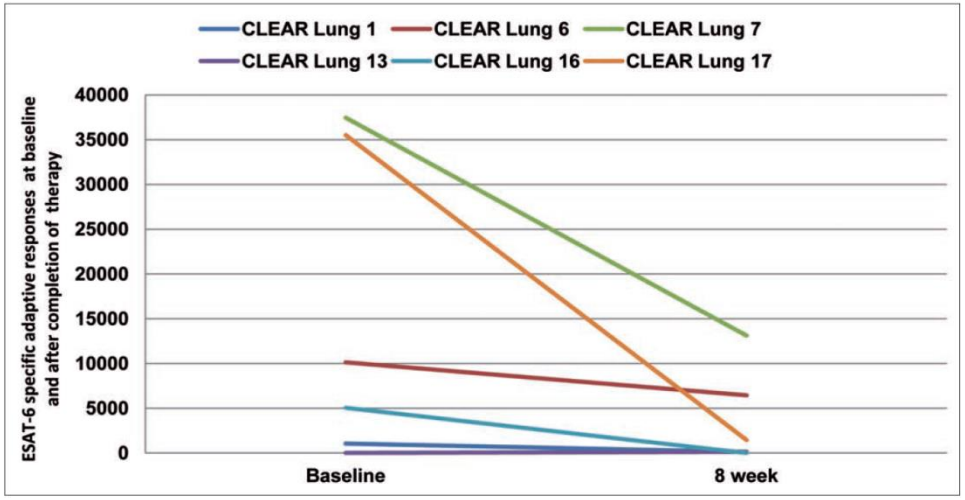
Serum amyloid A hypothesis



Chen ES. Nat Rev Rheumatol 2011

Effects of 8 weeks of CLEAR therapy in pulmonary sarcoidosis





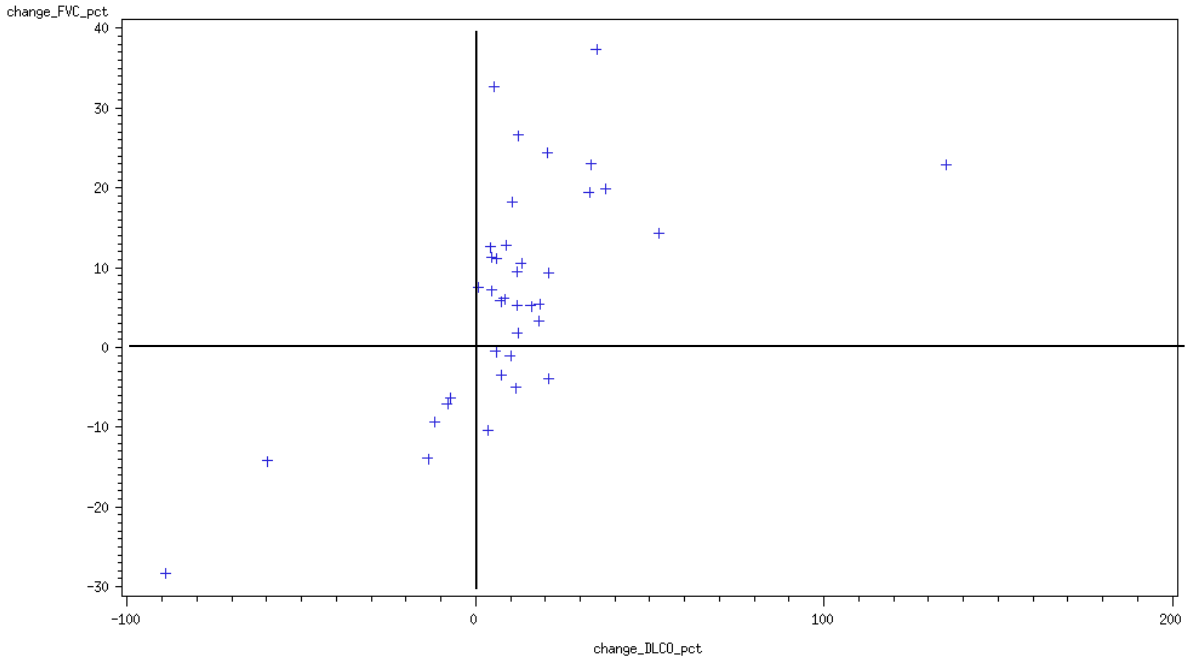
Drake WP. SVDLD 2014

Sarcoidosis trials

Trial	Target			
CLEAR	Non-tuberculous mycobacteria	Pulmonary	FVC	138
Nicotine	T-regs	Pulmonary	CT scan	50
ACTHAR gel	Melanocortin receptors	Pulmonary	Steroid toxicity	20
Dexamethasone	GR	All	HRQOL	76
Ustekinumab/ Golimumab	p40 subunit of IL12 and IL23	Pulmonary Cutaneous	FVC Global skin	173

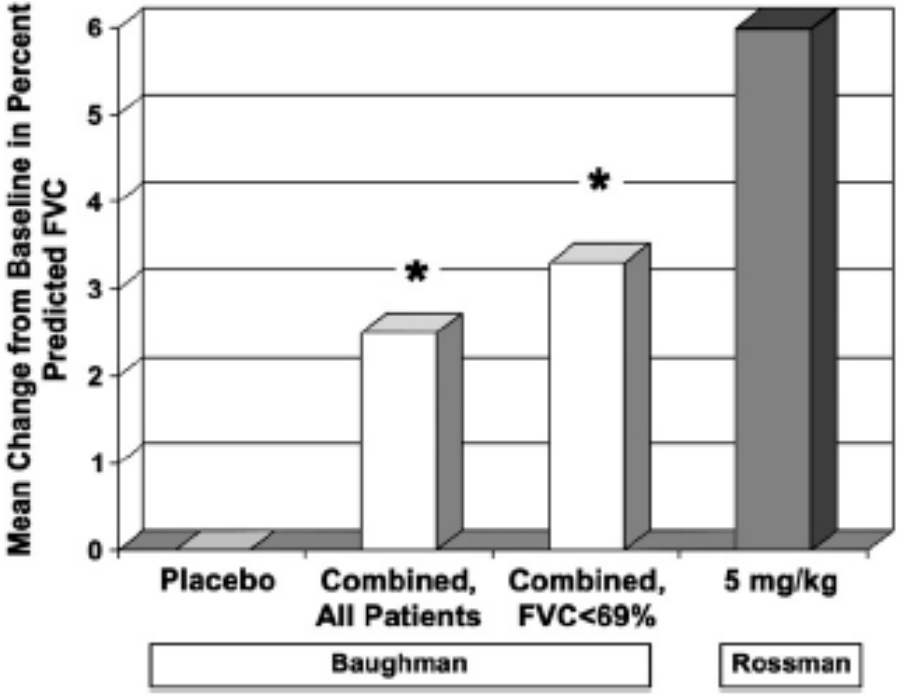
What is the magnitude of expected change in real life?

- n=53 patients treated with prednisone for 3-8 weeks
- Median FVC improvement 5.4%
- Median DLCO improvement was 10.3%
- >5% improvement of FVC was highly associated with improved MRC dyspnea and with patient global impression of benefit

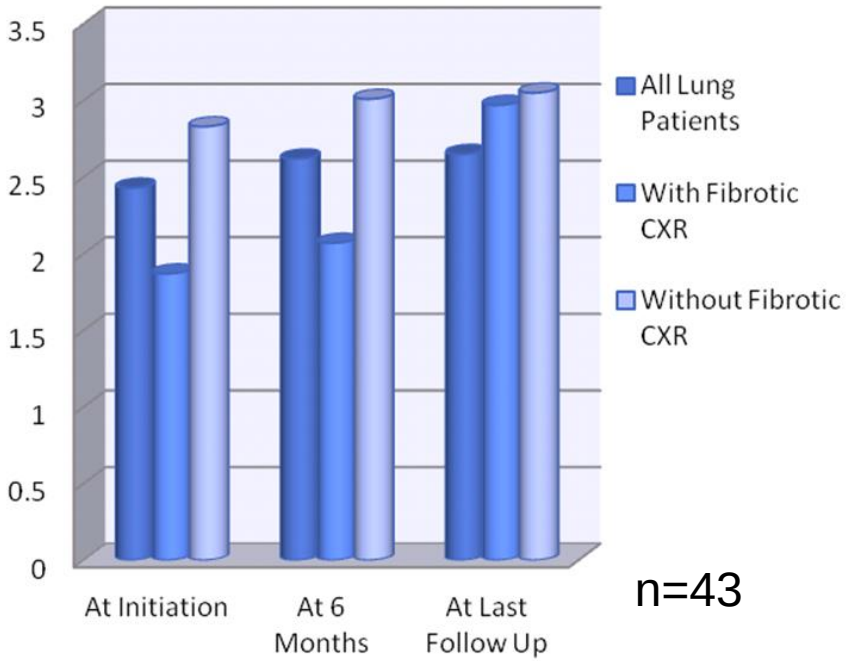


Magnitude of infliximab benefit on FVC

Clinical trials



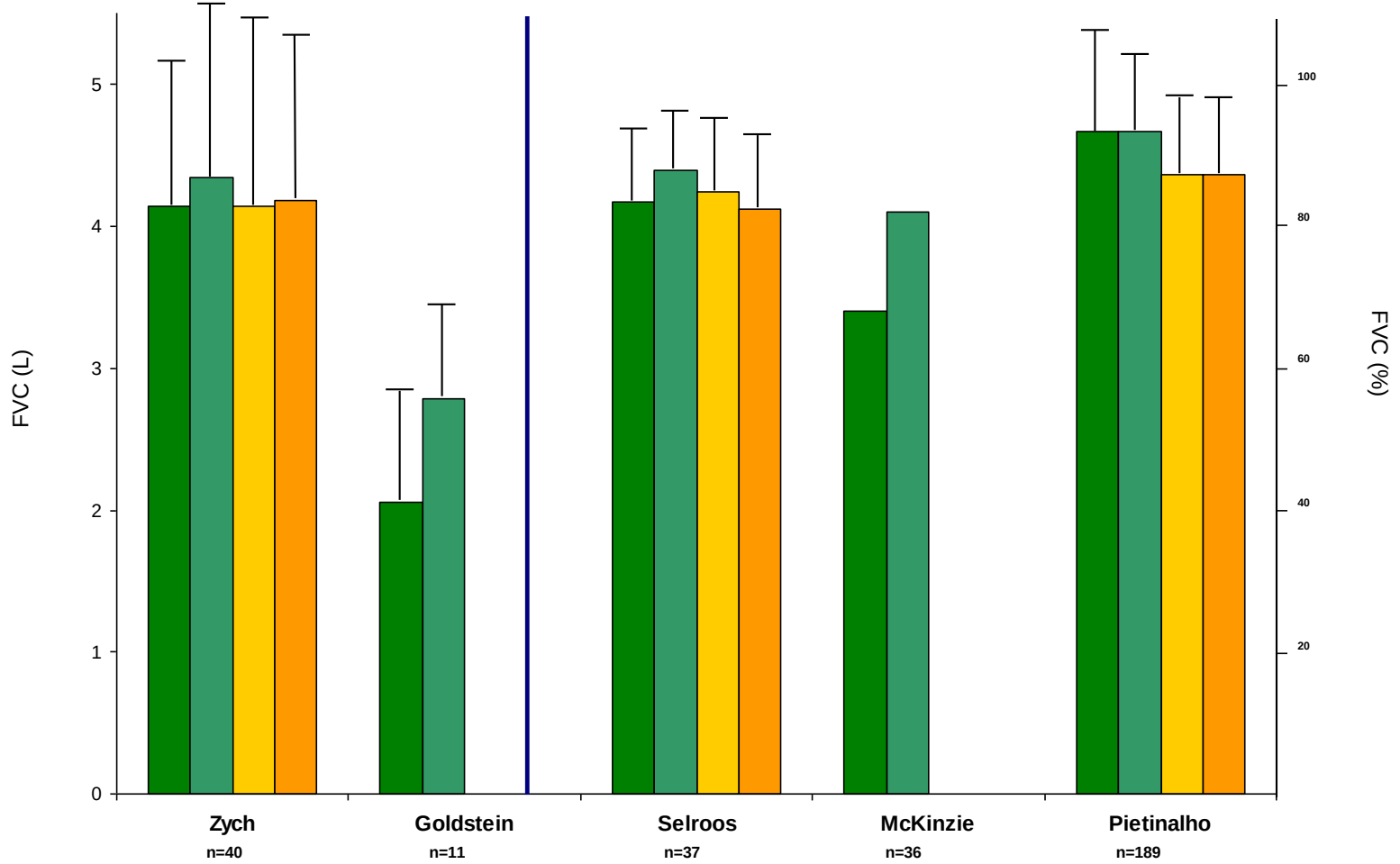
Cleveland Clinic experience



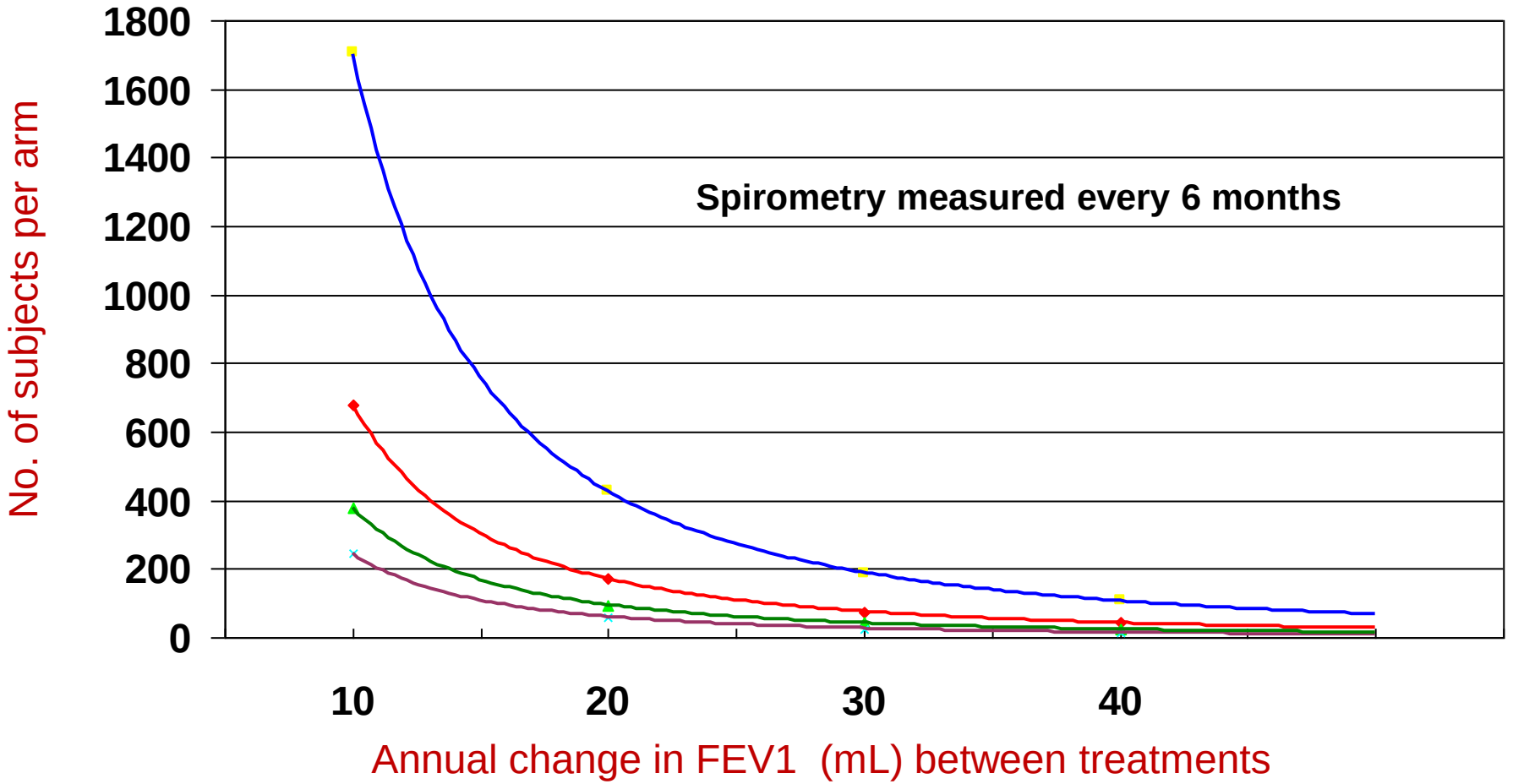
n=43

Baughman RP. Clin Chest Med 2008

Effect on FVC with variable study design

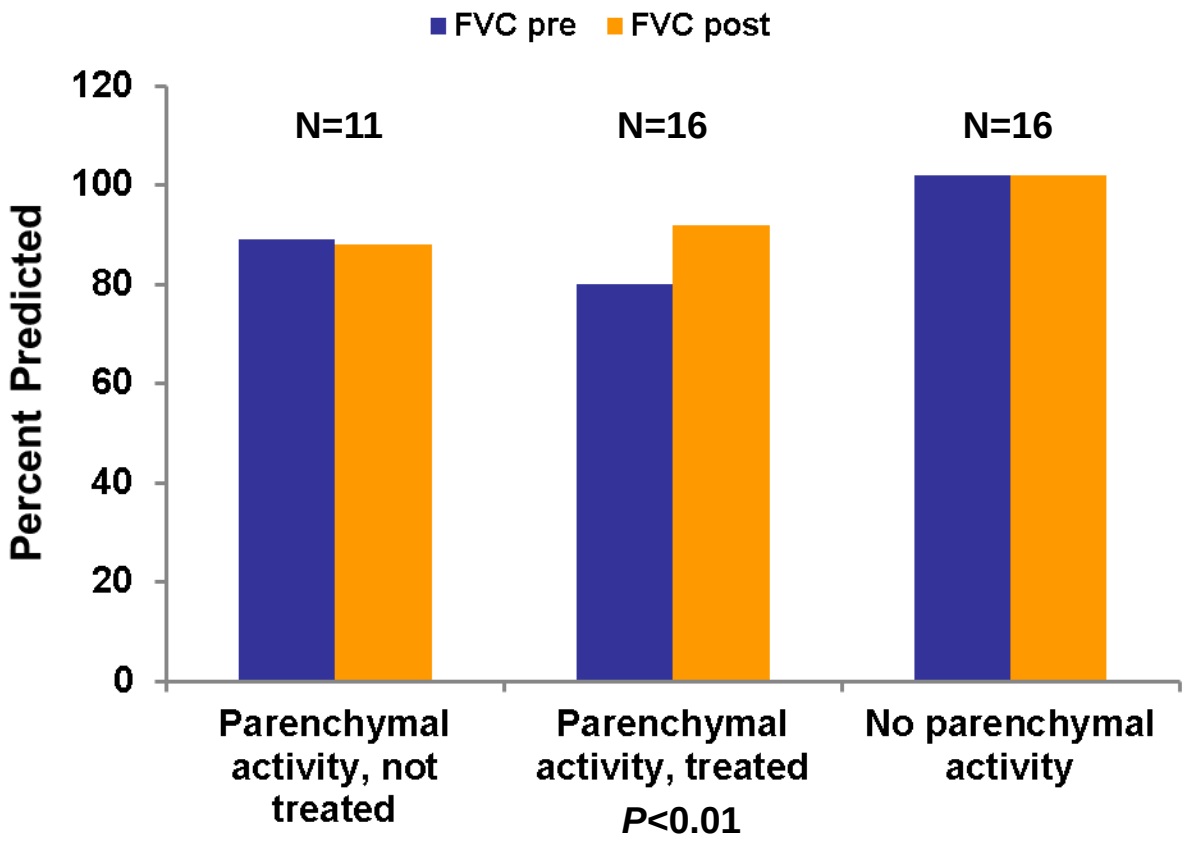


Sample size needed for various study durations in CWP



Wang M. Am J Respir Crit Care Med 2000

PET Scan Predicting Response to Therapy in Sarcoidosis: FVC Change



Keijsers RG Sarcoidosis Vasc Diffuse Lung Dis. 2011

Clinical study considerations

- Population
  - Population likely to progress
  - Equipoise about placebo versus treatment
  - Enrich for activity
- Endpoint
  - FVC—compare placebo versus drug—two sided
  - Need for therapy escalation
  - Composite of clinical deterioration (TTCW)
  - Surrogate (biologic, PET)
  - PRO

Steroid dose in practice

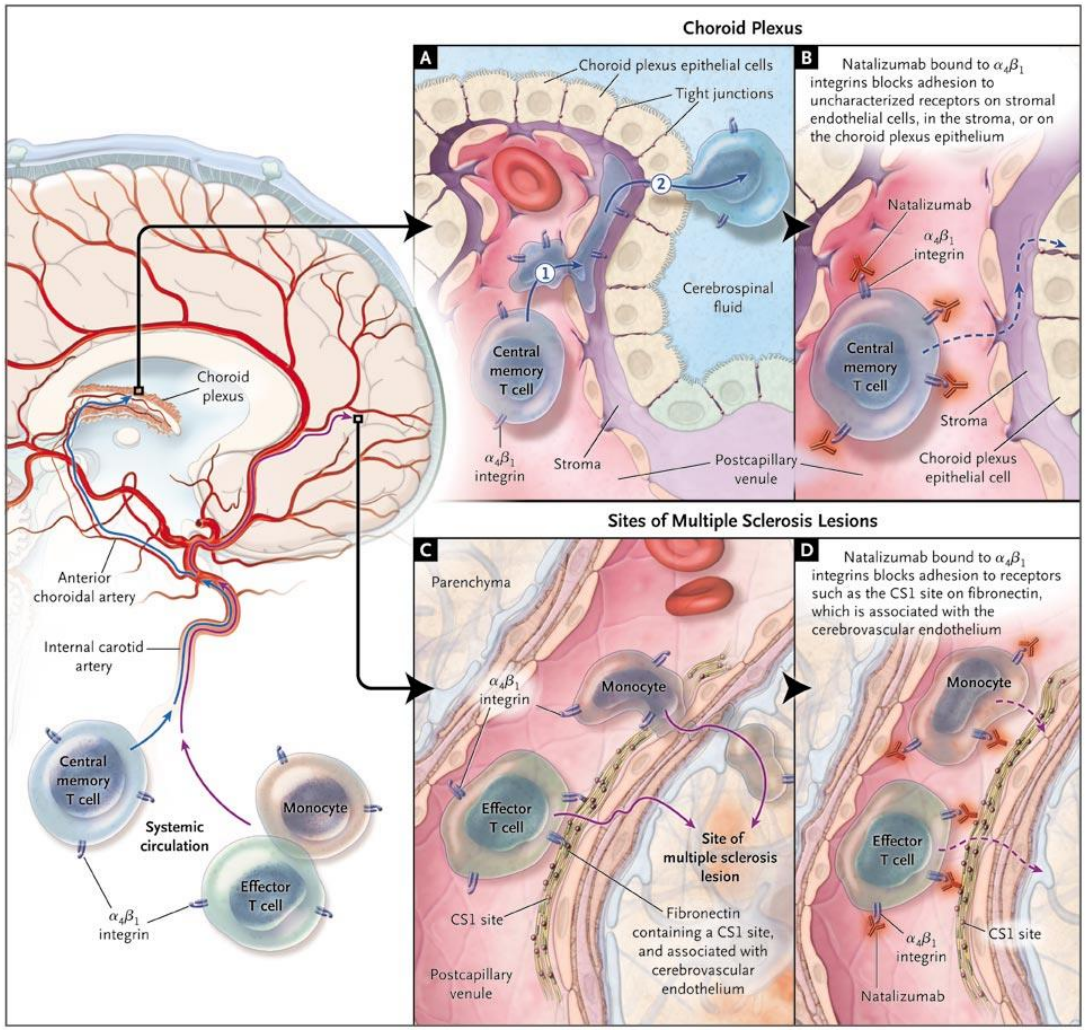
- Chronic dosing in Johns Hopkins cohort[1]
  - 91% ≤ 15 mg
  - 65% ≤ 10 mg
- Infliximab trial (n=122/138)[2]
  - median dose 10 mg/d (2-50 mg/d)
- Golimumab/ustekinumab trial (n=131/173)[2]
  - median dose 10 mg/d (2-30 mg/d)

1Johns CJ. Ann NY Acad Sci 1986

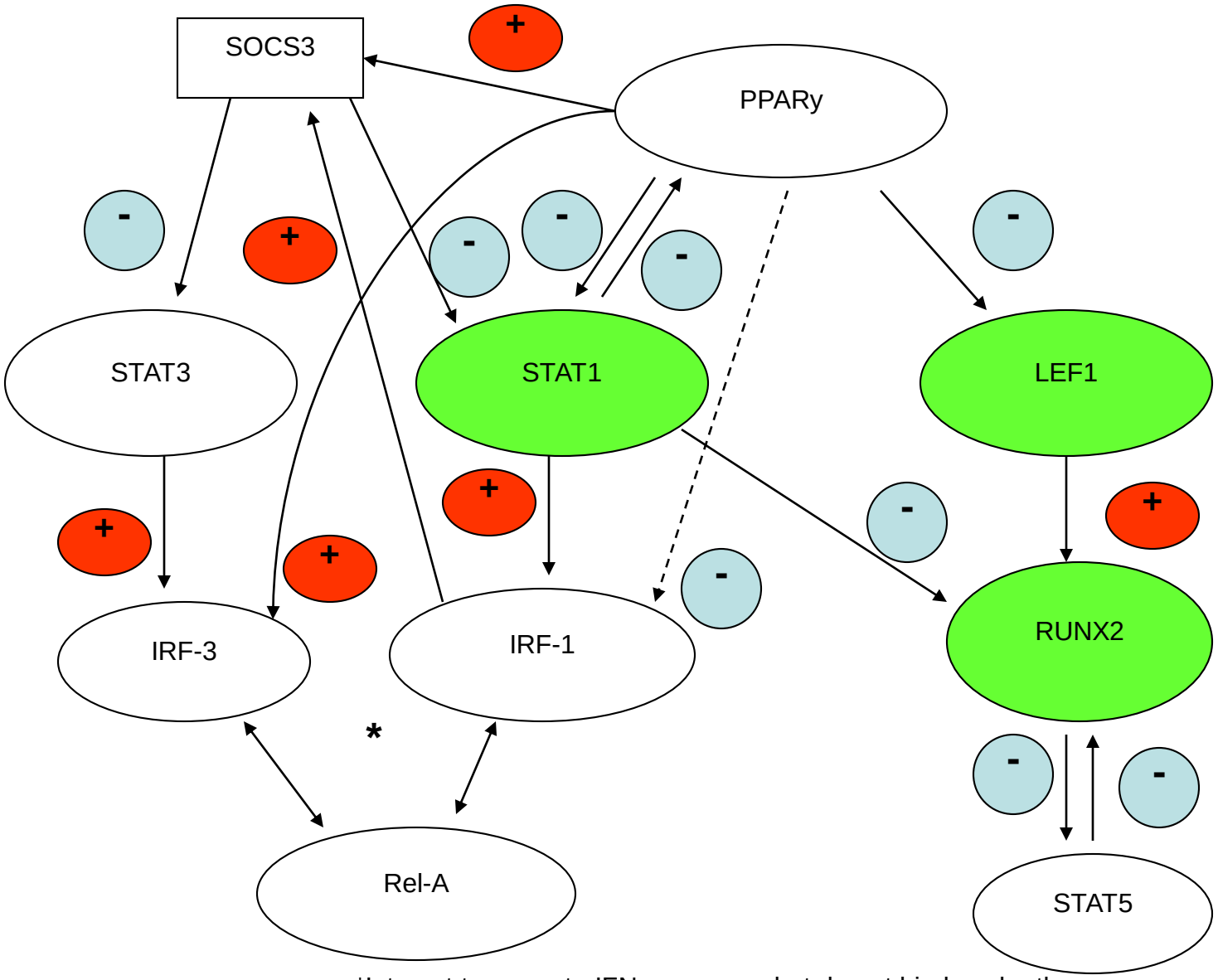
2Rosemary Watt, personal communication

Steroids are associated with impaired QOL

Lymphocyte trafficking in the CNS

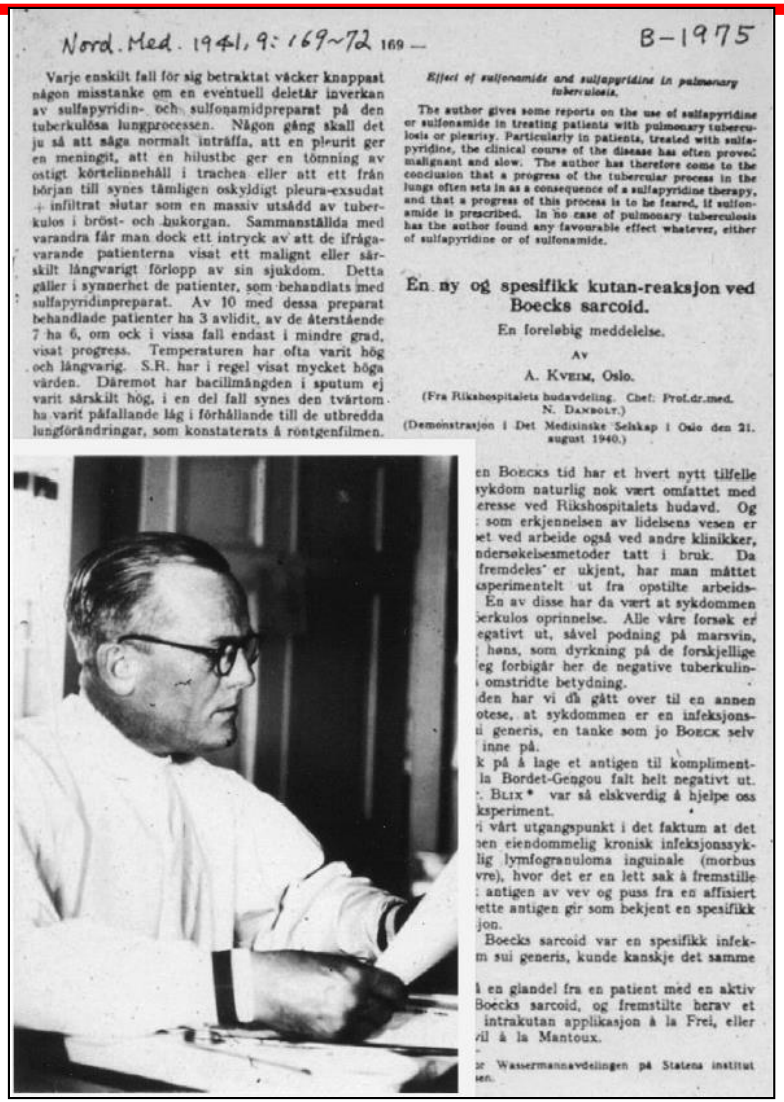


Ransohoff R. N Engl J Med 2007



*Interact to promote IFN responses but do not bind each other.

Louis Siltzbach and the Kveim-Siltzbach test



Nord. Med. 1941, 9: 169–72 169 — B–1975

Varje enskilt fall för sig betraktat väcker knappast någon misstanke om en eventuell deletär inverkan av sulfapyridin- och sulfonamidpreparat på den tuberkulösa lungprocessen. Någon gång skall det ju så att säga normalt inträffa, att en pleurit ger en meningit, att en hilustbc ger en tömning av ostigt körtelinnehåll i trachea eller att ett från början till synes tämligen oskyldigt pleura-exsudat + infiltrat slutar som en massiv utsådd av tuberkulos i bröst- och bukorgan. Sammanställda med varandra får man dock ett intryck av att de ifrågavarande patienterna visat ett malignt eller särskilt långvarigt förlopp av sin sjukdom. Detta gäller i synnerhet de patienter, som behandlats med sulfapyridinpreparat. Av 10 med dessa preparat behandlade patienter ha 3 avlidit, av de återstående 7 ha 6, om ock i vissa fall endast i mindre grad, visat progress. Temperaturen har ofta varit hög och långvarig. S.R. har i regel visat mycket höga värden. Däremot har bacillmängden i sputum ej varit särskilt hög, i en del fall synes den tvärtom ha varit påfallande låg i förhållande till de utbredda lungförändringar, som konstaterats å röntgenfilmen.

Effect of sulfonamide and sulfapyridine in pulmonary tuberculosis.

The author gives some reports on the use of sulfapyridine or sulfonamide in treating patients with pulmonary tuberculosis or pleurisy. Particularly in patients, treated with sulfapyridine, the clinical course of the disease has often proved malignant and slow. The author has therefore come to the conclusion that a progress of the tuberculer process in the lungs often sets in as a consequence of a sulfapyridine therapy, and that a progress of this process is to be feared, if sulfonamide is prescribed. In no case of pulmonary tuberculosis has the author found any favourable effect whatever, either of sulfapyridine or of sulfonamide.

En ny og spesifikk kutan-reaksjon ved Boecks sarcoid.

En foreløbig meddelelse.

Av

A. Kveim, Oslo.

(Fra Rikshospitalets hudavdeling. Chef: Prof.dr.med. N. Danbolt.)

(Demonstrasjon i Det Medisinske Selskap i Oslo den 21. august 1940.)

en Boecks tid har et hvert nytt tilfelle sykdom naturlig nok vært omfattet med eresse ved Rikshospitalets hudavd. Og som erkjennelsen av lidelsens vesen er et ved arbeide også ved andre klinikker, ndersøkelsesmetoder tatt i bruk. Da fremdeles er ukjent, har man måttet asperimentelt ut fra opstilte arbeids- En av disse har da vært at sykdommen berkulos oprinnelse. Alle våre forsøk er egativt ut, såvel podning på marsvin, høns, som dyrkning på de forskjellige eg forbigår her de negative tuberkulin- omstridte betydning.

den har vi då gått over til en annen otese, at sykdommen er en infeksjons- i generis, en tanke som jo Boeck selv inne på.

k på å lage et antigen til kompliment- la Bordet-Gengou falt helt negativt ut. . Blix * var så elskverdig å hjelpe oss ksperiment.

i vårt utgangspunkt i det faktum at det en eiendommelig kronisk infeksjonssyk- lig lymfogranuloma inguinale (morbus vre), hvor det er en lett sak å fremstille antigen av vev og puss fra en affisiert ette antigen gir som bekjent en spesifikk jon.

Boecks sarcoid var en spesifikk infek- m sui generis, kunde kanskje det samme

en glandel fra en patient med en aktiv Boecks sarcoid, og fremstilte herav et intrakutan applikasjon å la Frei, eller il å la Mantoux.

r Wassermannavdelingen på Statens institut en.

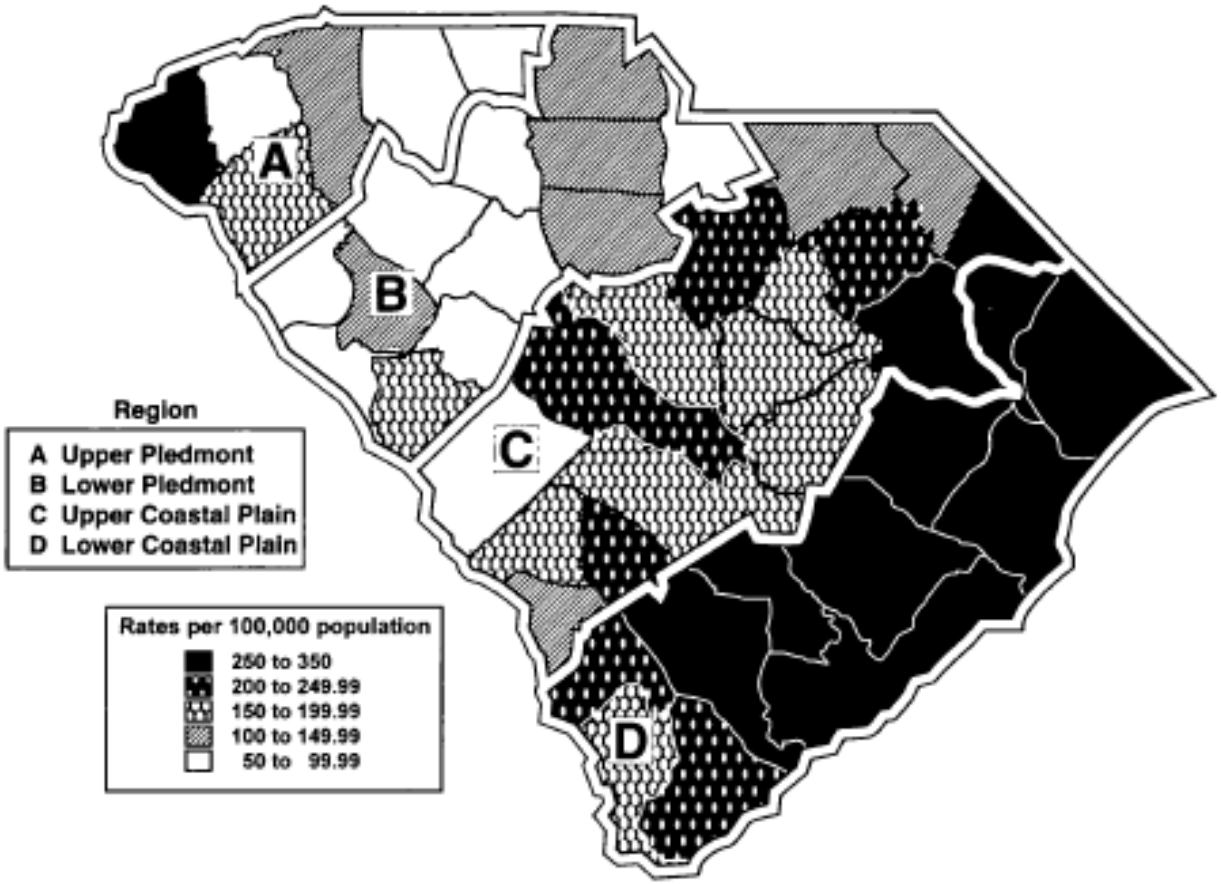
- Recapitulated granulomatous reaction
  after intradermal injection of spleen
  or LN
- Clonal T-cell population in granulomas
- Insoluble and resistant to heat, acid, nucleases and proteases

Sharma OP. Clin Dermatol 2007

Evidence for a transmissible etiology

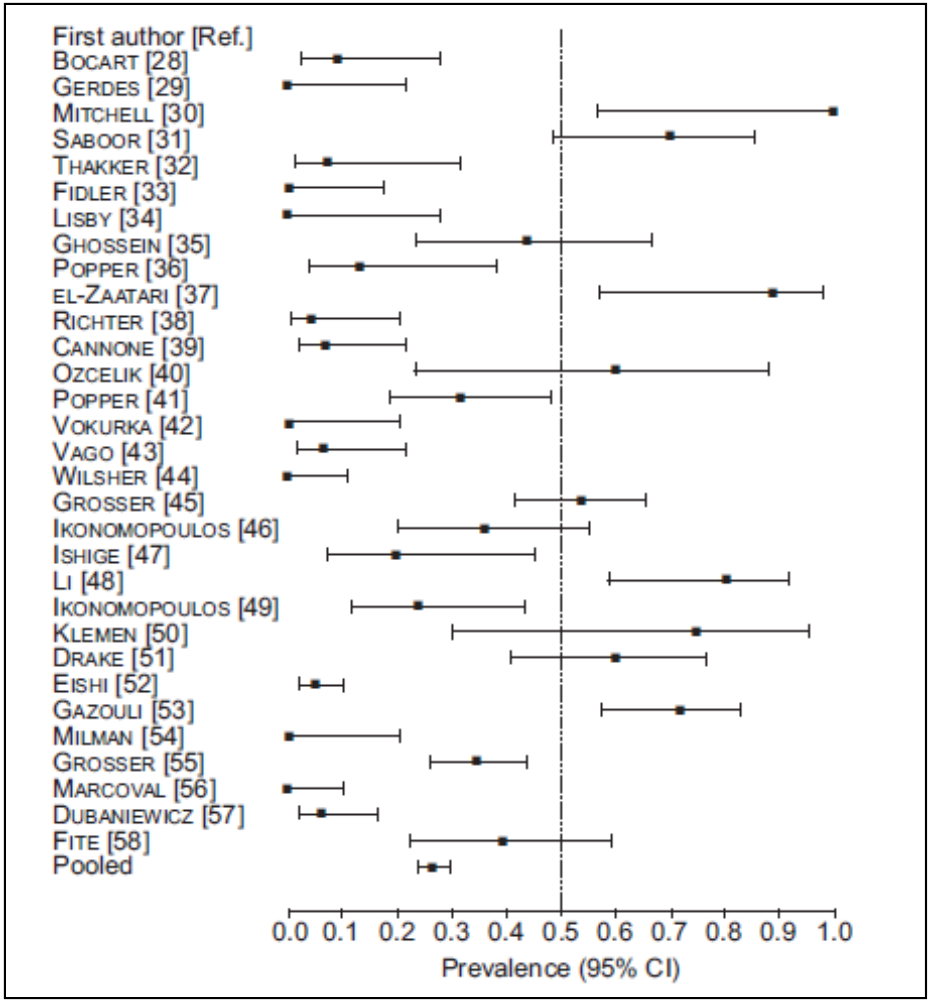
- Analogy with granulomatous lung diseases
- Reproducibility with Kveim reagent
- Case-clustering (nurses, Naval personnel)
- Epidemiologic data (Isle of Man)
- Transmission by transplant (heart, lung, bone marrow)

Geographic variance: hospitalization for sarcoidosis



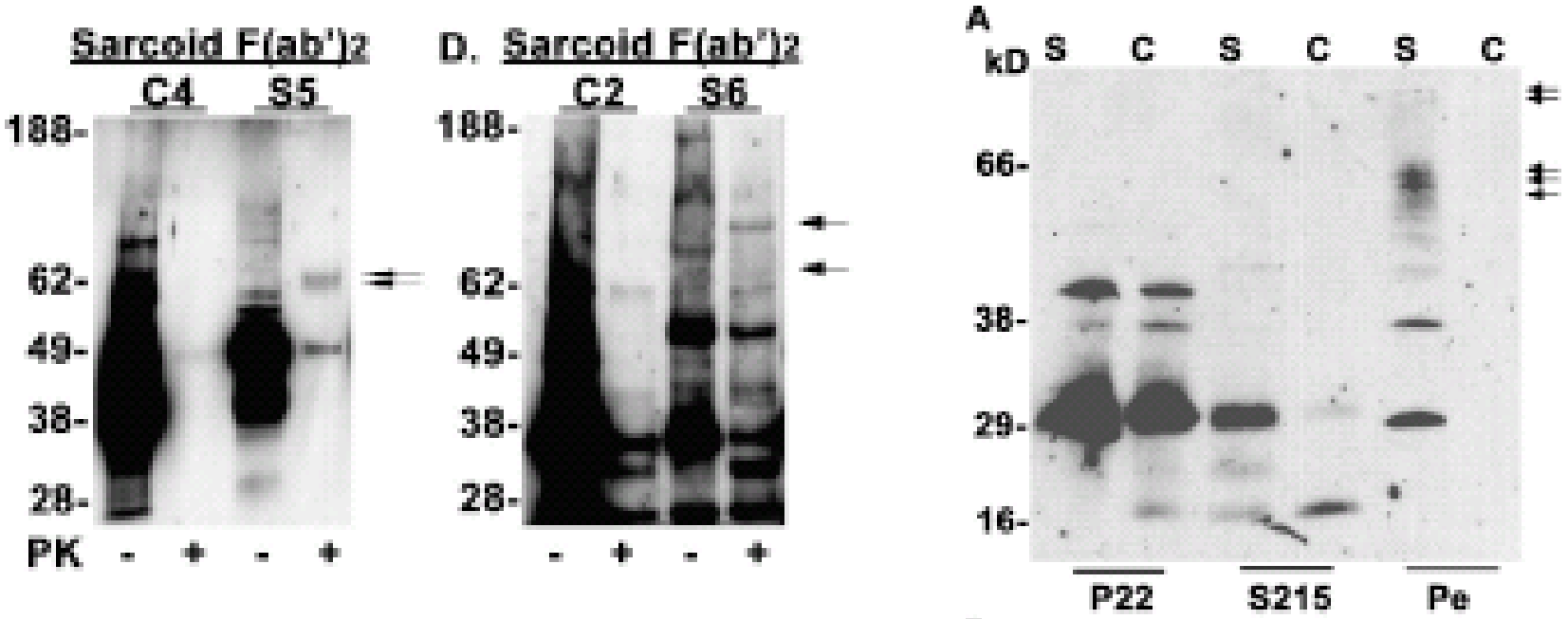
Kajdasz DK. Am J Epidemiol 1999

Multiple attempts to isolate mycobacterial DNA



Gupta D. Eur Respir J 2007

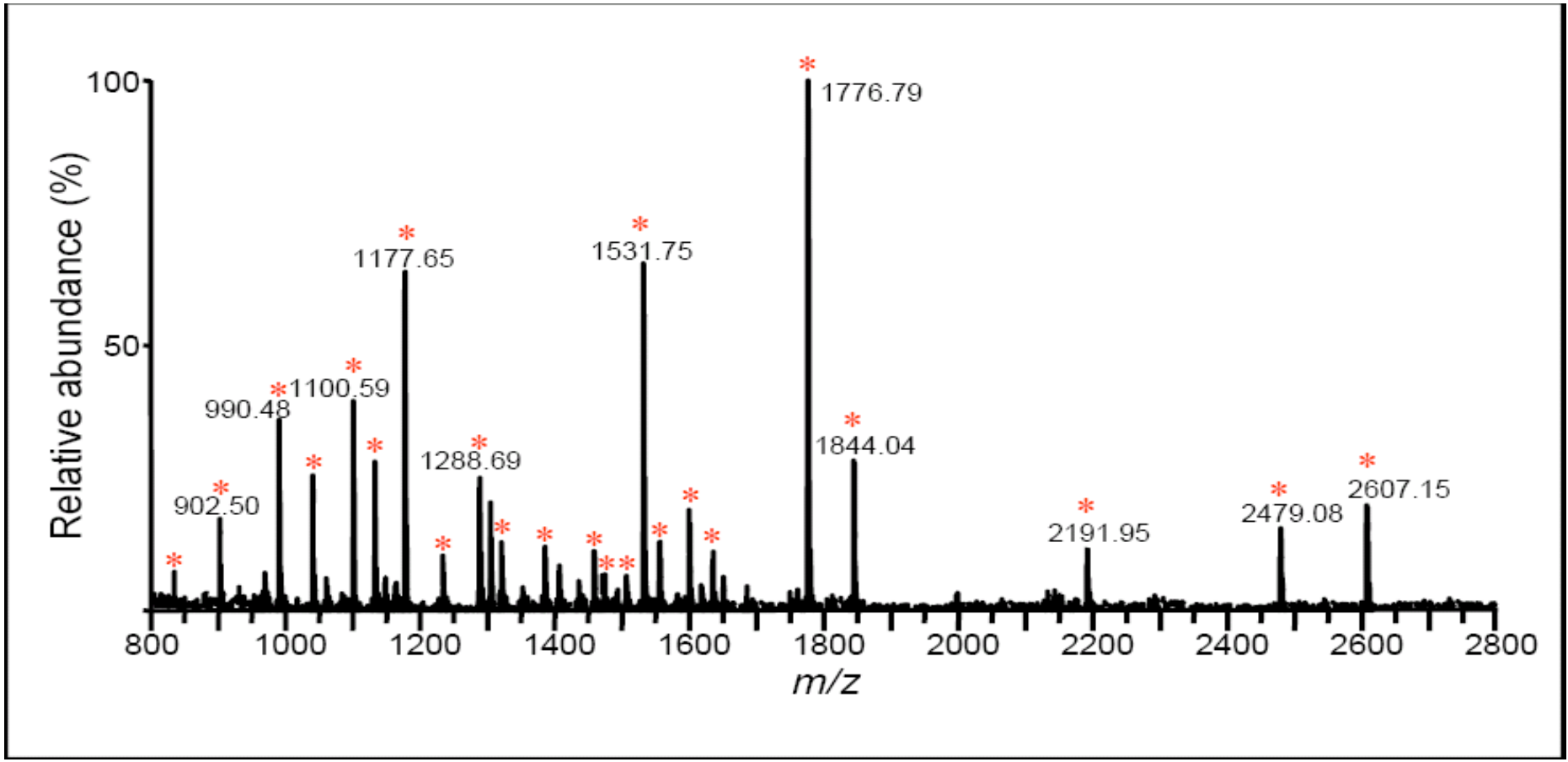
Identification of humoral immunity against sarcoidosis protein extracts



Pooled IgG from sarcoidosis patients only binds unidentified proteins in extracts of sarcoidosis tissues. The protein fraction is poorly soluble and protease resistant, consistent with known properties of the Kveim-Siltzbach reagent

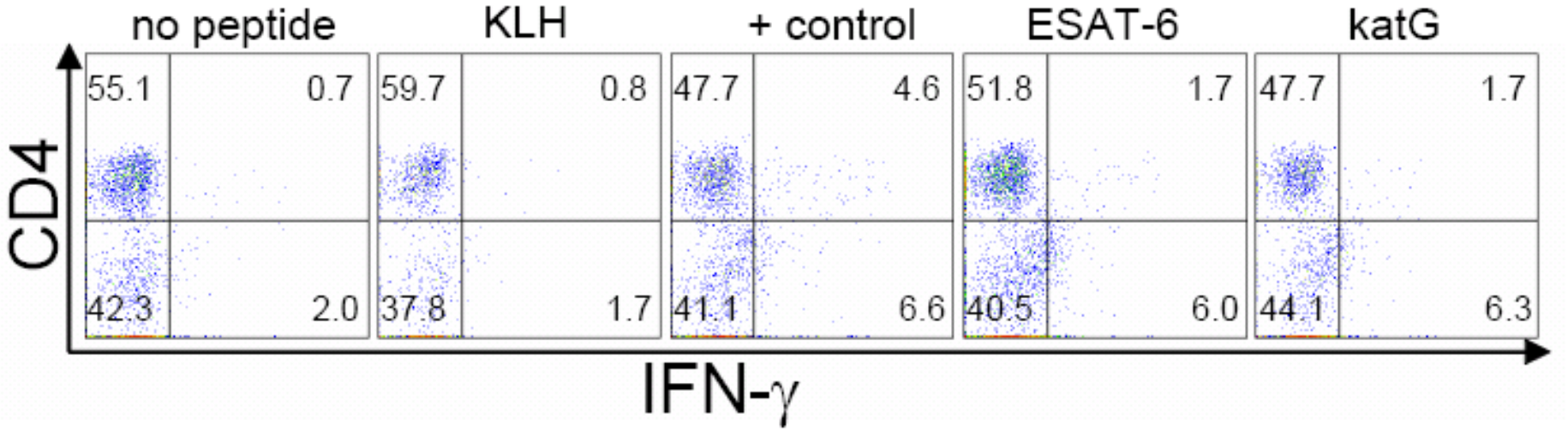
Song Z. J Exp Med 2005

Peptide signature



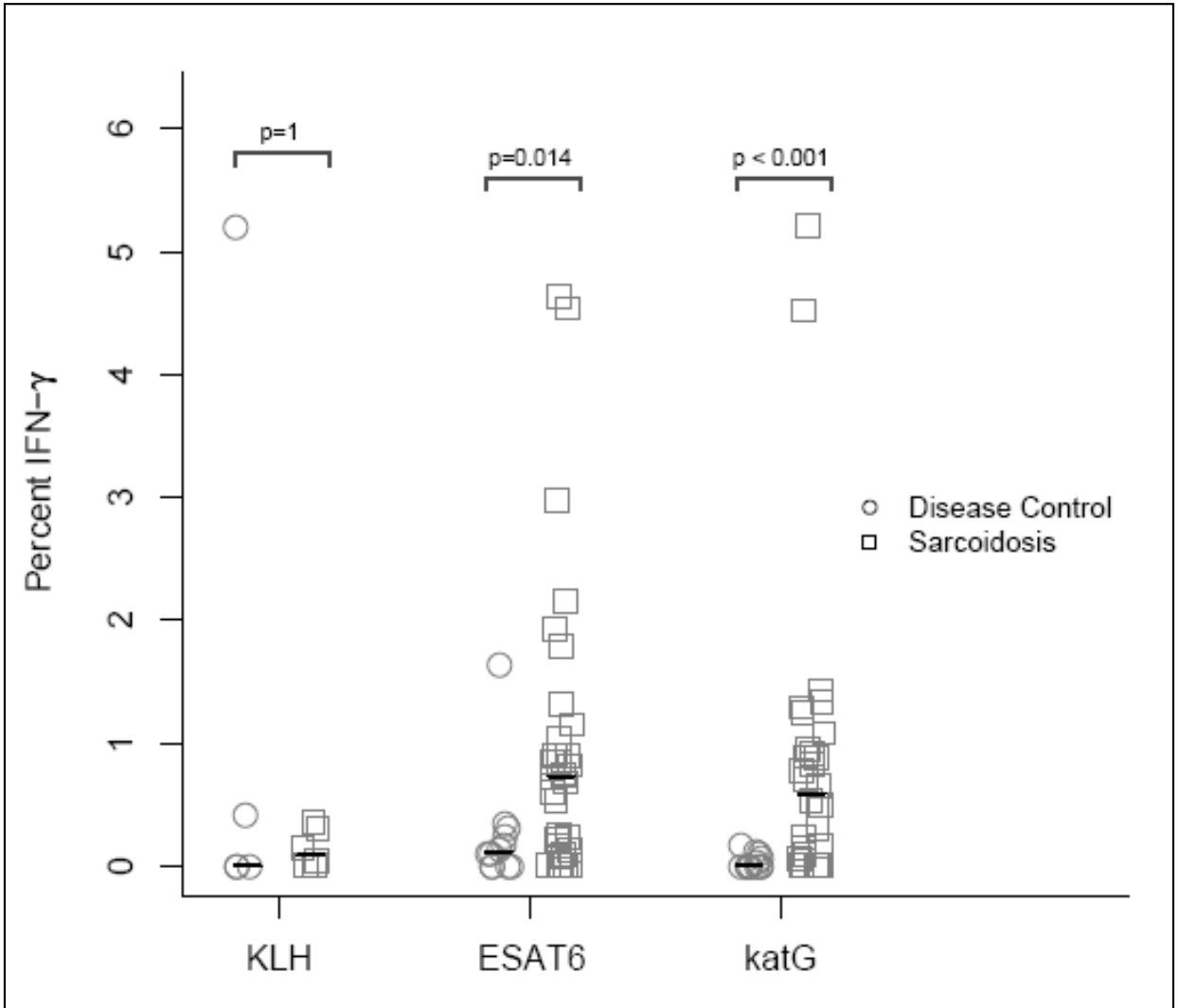
Mycobacterial catalase-peroxidase in 5/9 sarcoid tissues

CD4 responses to mycobacterial antigens in sarcoidosis BAL cells

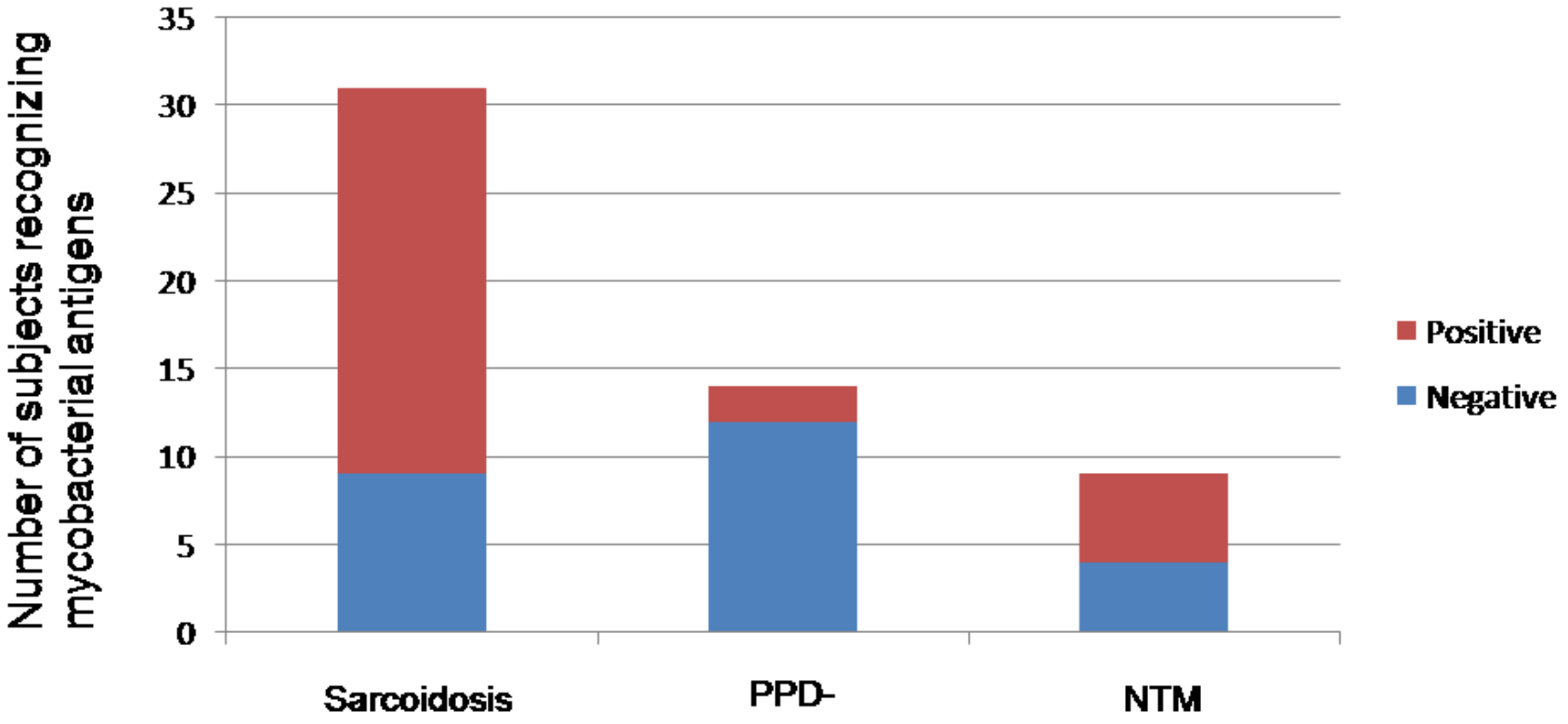


Richter K. Infect Immun 2009

CD4+ responses in 2/3 of subjects

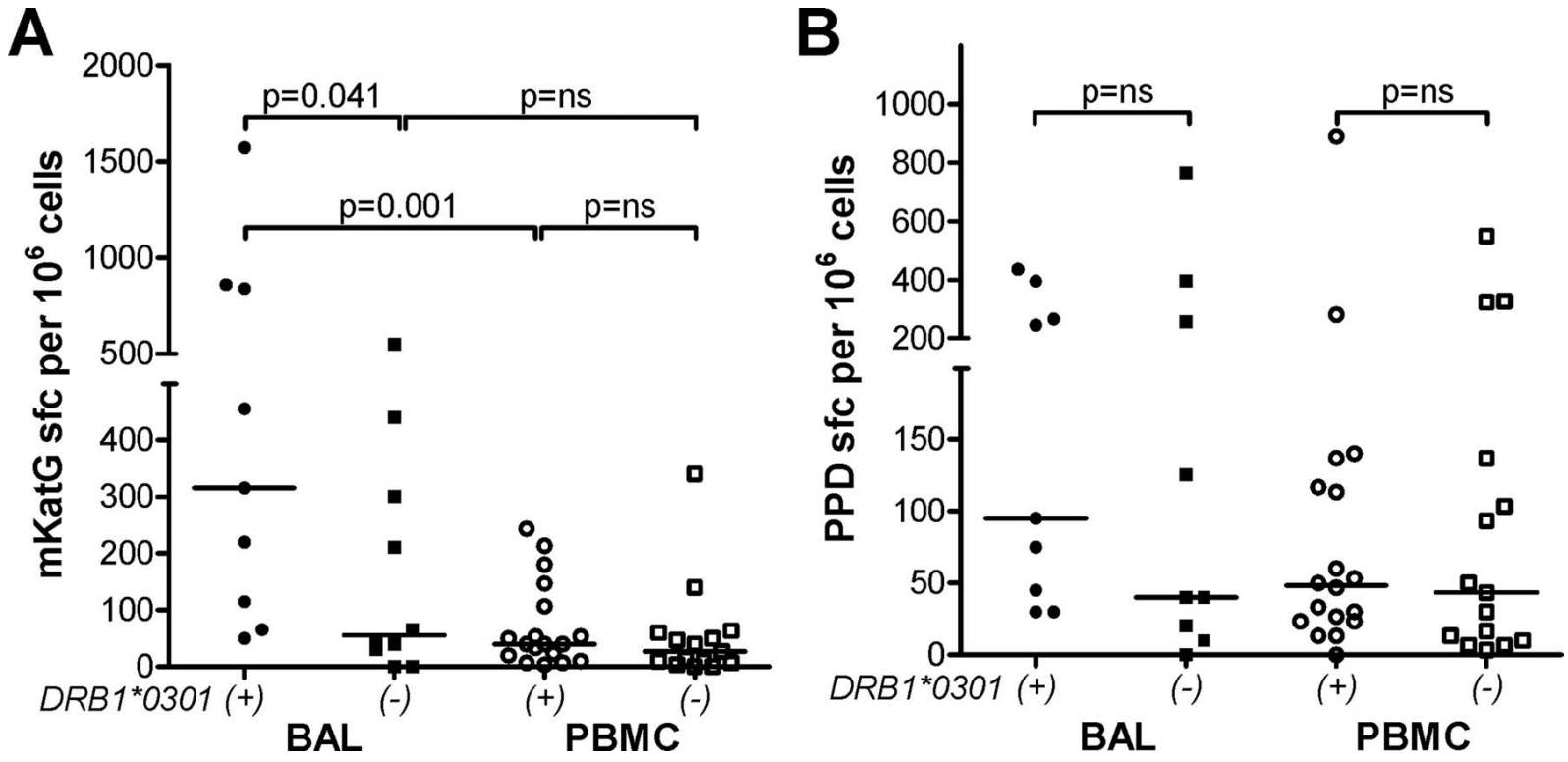


Sarcoidosis patients respond to multiple antigens



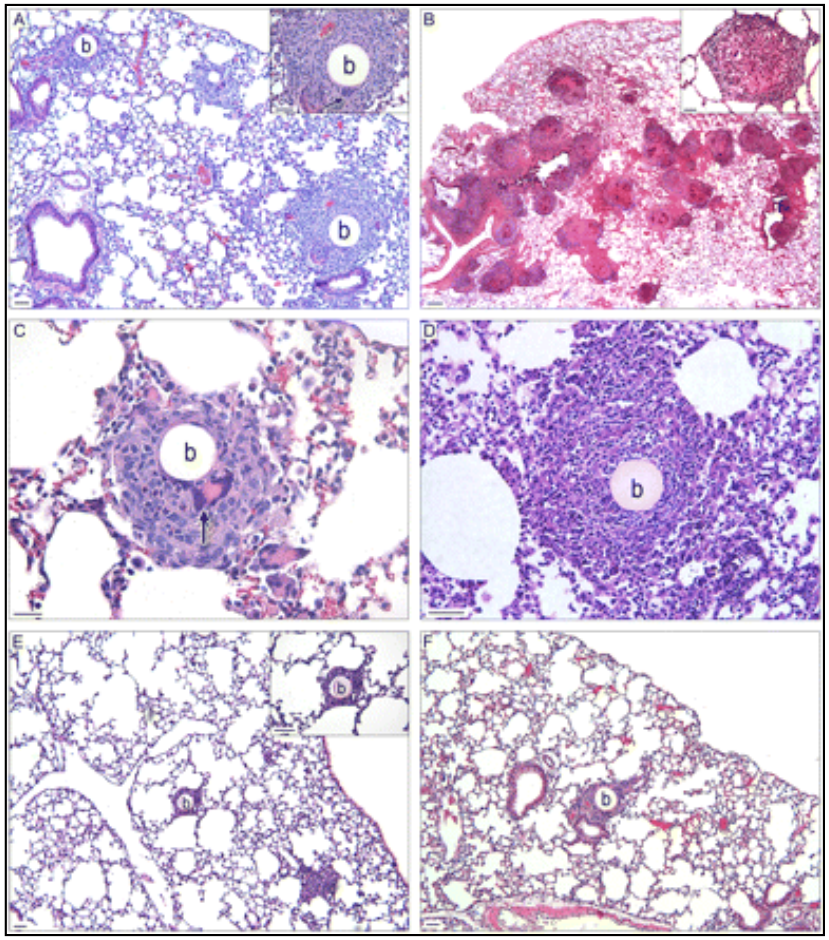
Oswald-Richter KA. Respir Res. *In press*

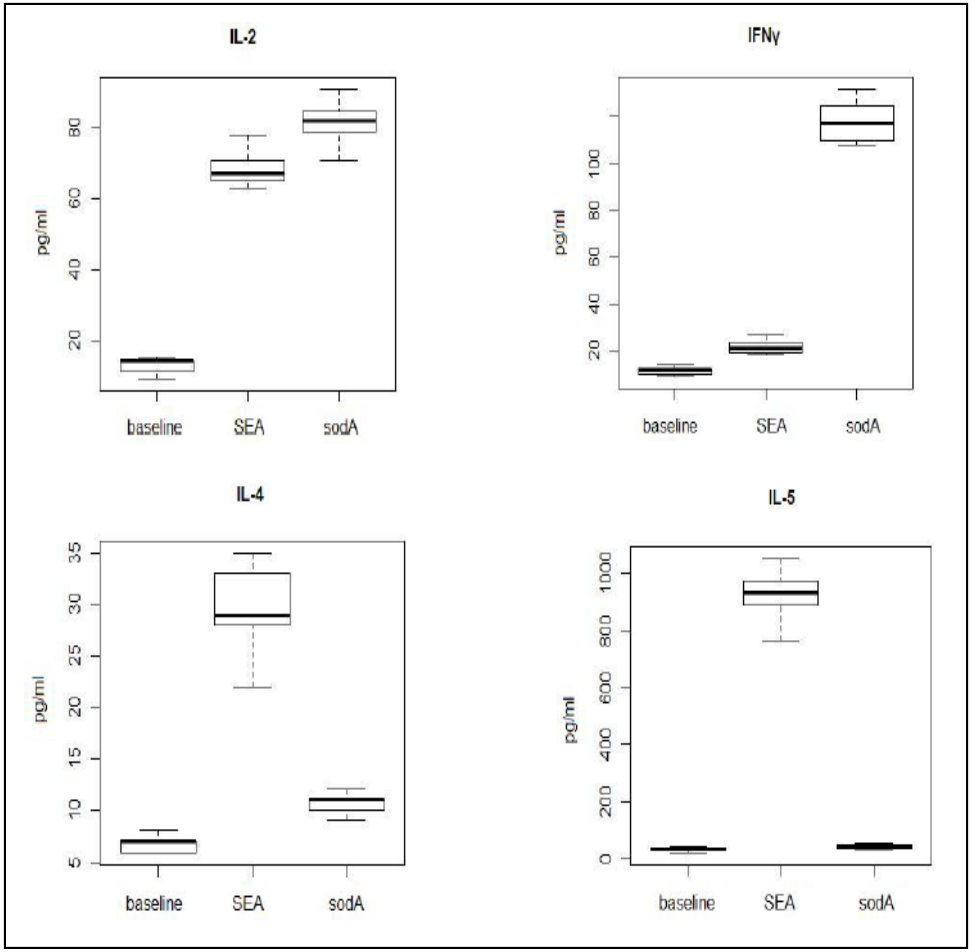
T-cell response depend on HLA type



Chen ES. J Immunol 2008

Sarcoidosis Murine Lung Granuloma Model Using *Mycobacterium* Superoxide Dismutase A Peptide





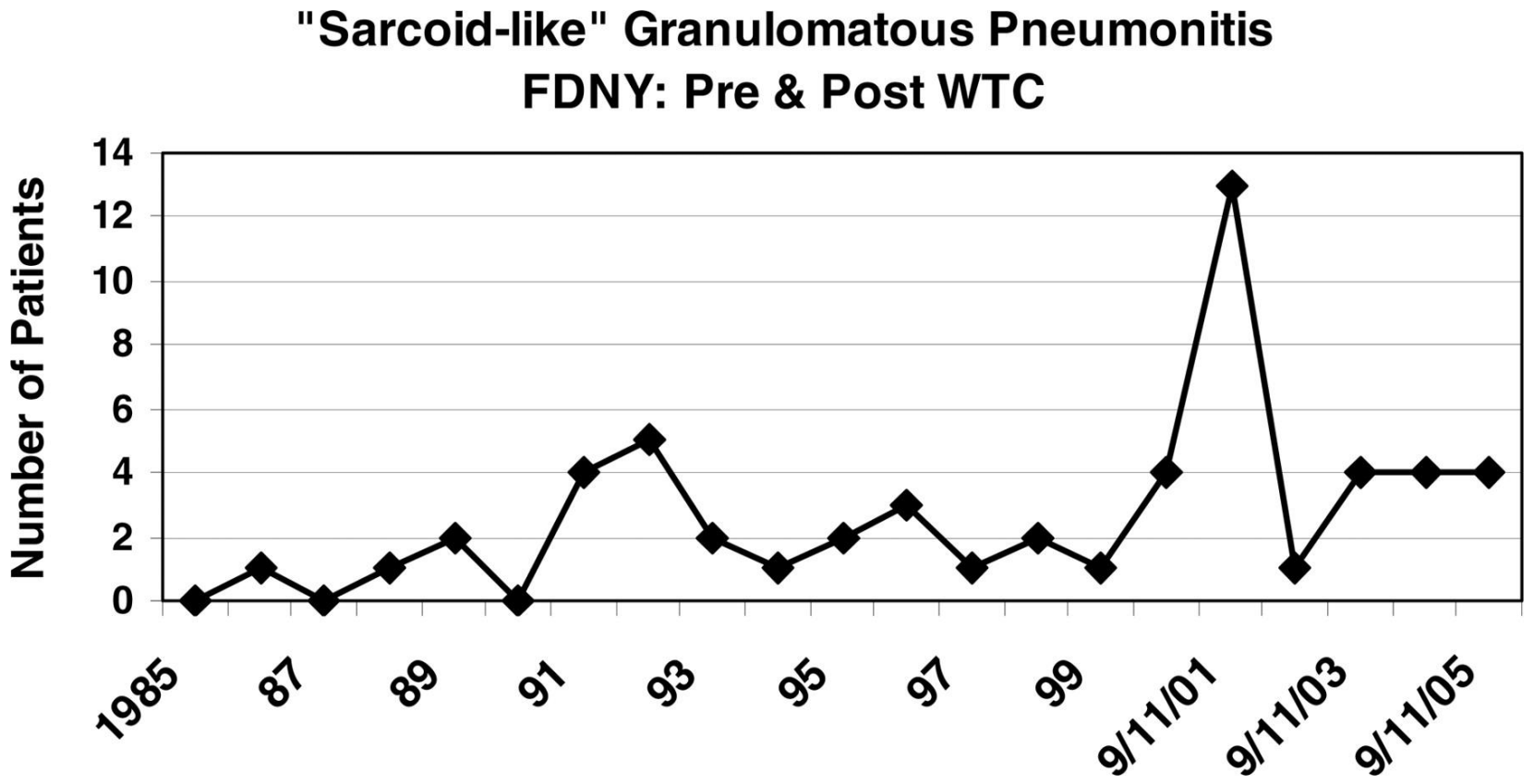
Swaisgood CM. Am J Respir Cell Mol Biol 2011

Association with rural exposures

Exposure	Exposure profile	% cases (n = 44)[a]	% controls (n = 88)[a]	Unadjusted OR with 95% CI	Adjusted OR[b] with 95% CI
Use of a coal stove	Yes	22.7	4.5		
	No	77.3	95.5	6.2 [1.7, 22.7]	3.3 [0.9, 12.8]
Use of a wood stove	Yes	63.6	27.3		
	No	34.1	72.7	4.1 [1.9, 9.0]	3.7 [1.5, 8.8]
Use of a fireplace	Yes	54.5	26.1		
	No	43.2	73.9	5.5 [2.0, 14.9]	6.8 [2.1, 21.8]
Use of or exposure to insecticides and/or herbicides other than for home extermination	Yes	31.8	17.0		
	No	68.2	83.0	2.1 [0.9, 4.7]	2.0 [0.8, 5.1]
Use of well or spring water	Yes	50.0	29.5		
	No	47.7	70.5	2.2 [1.1, 4.7]	2.4 [1.0, 5.6]
Living or working on a farm	Yes	27.3	10.2		
	No	70.5	89.8	3.4 [1.2, 9.1]	3.1 [1.1, 8.9]

Kajdasz DK. Ann Epidemiol 2001

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

ACE versus other prognostic markers in pulmonary sarcoidosis

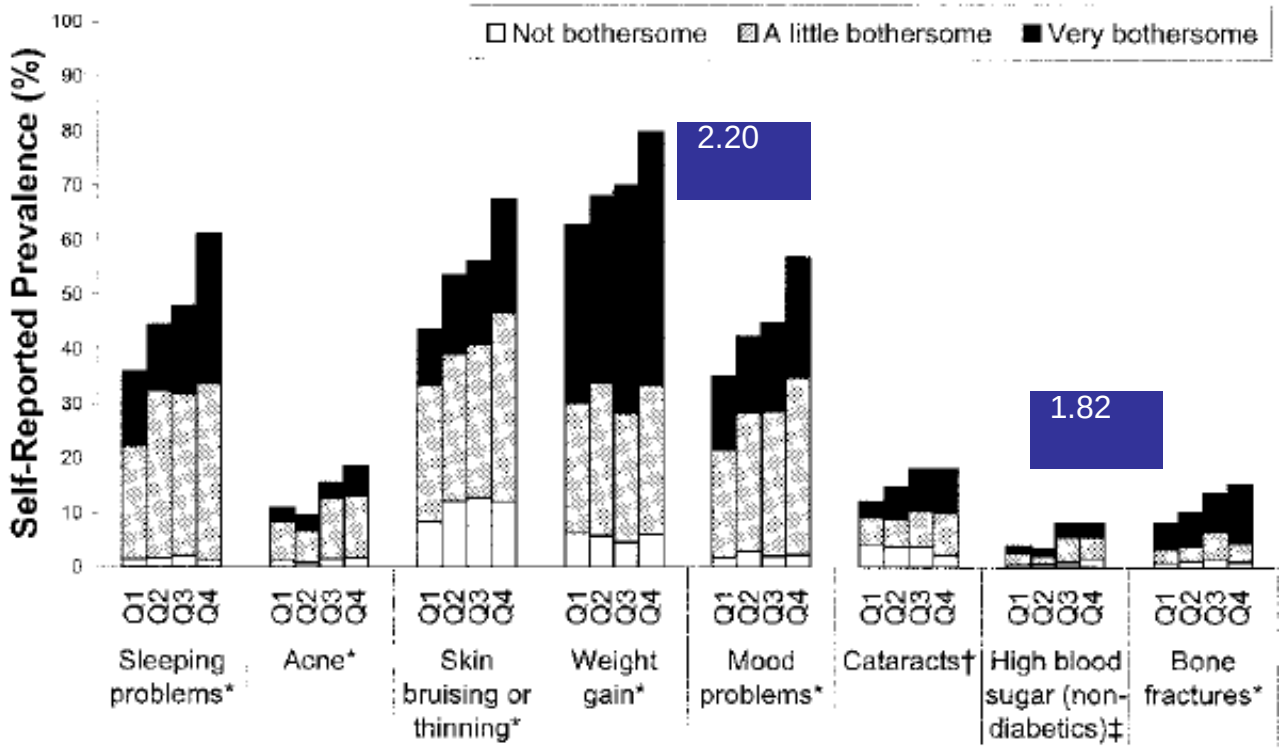
Risk of increasing infiltrates

Parameters	AUC	Cut-Off Level	Sensitivity (%)	Specificity (%)	Discriminative Value (%)
SAA	0.444	9.3	38.5	73.3	62.8
sIL-2R	0.758	1,195	61.5	73.3	69.8
Lysozyme	0.692	11.25	76.9	66.7	69.8
ACE	0.613	17.95	76.9	50	58.1
KL-6	0.836	354	76.9	70	72.1
Total cells	0.633	1.80	76.9	56.7	62.8
AM	0.574	1.73	46.2	73.3	65.1
Ly	0.669	0.52	69.2	70	69.8
Neu	0.456	0.01	76.9	36.7	48.8
Eo	0.435	0.01	30.8	76.7	62.8

Miyoshi S. Chest 2010

Rate of eight complications in individuals using GC > 60 days

n=2167 patients



Curtis JR. Arthritis Rheum 2006

HRQL in 114 sarcoidosis patients versus steroid dose

< 500 mg vs. > 500 mg of prednisone over the prior year

Table 3 Mean scores after propensity score matching by the two corticosteroid dose groups*.

PRO module	>500 mg prednisone/year	<=500 mg prednisone/year	Minimum important difference**	p-Value
SHQ total [+]	4.18 (0.37)	4.17 (0.33)	N/A	0.88
SHQ physical [+]	4.73 (0.70)	4.46 (0.69)	N/A	0.05
SHQ daily [+]	4.01 (0.41)	4.17 (0.48)	N/A	0.08
SHQ emotional [+]	3.79 (0.51)	3.81 (0.45)	N/A	0.35
SAT pain [−]	54.5 (10.0)	51.8 (10.1)	3.2	0.18
SAT fatigue [−]	54.8 (114)	48.9 (10.6)	3.1	<0.0001
SAT satisfaction [+]	46.5 (10.7)	51.5 (11.8)	3.0	0.03
SAT daily activities [+]	42.1 (7.5)	45.8 (9.5)	3.0	0.03
SAT lung [−]	45.7 (9.1)	42.7 (9.5)	2.7	0.12

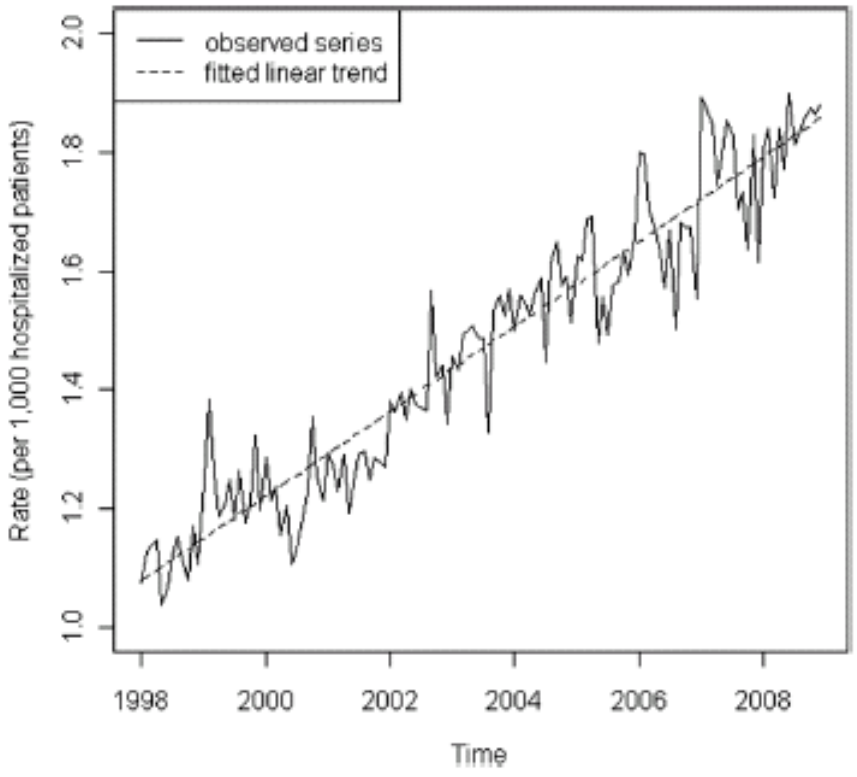
Judson MA. Respir Med 2015

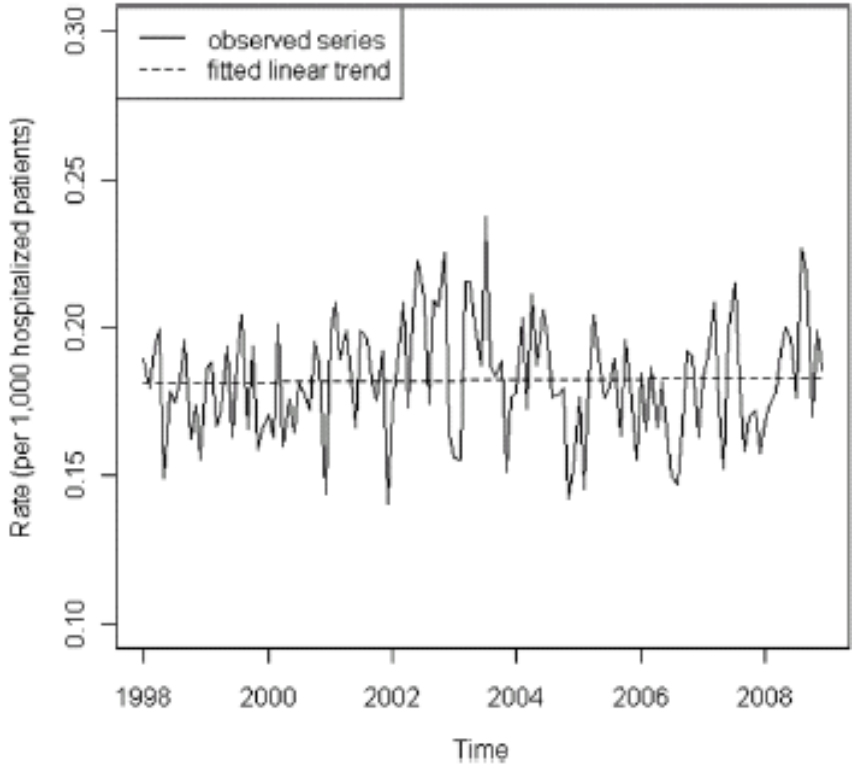
Impact of higher steroid use on health care encounters

- Adjusted OR for more than 50% median (2.9 grams) CS exposure
  - Visit related to sarcoidosis 3.09 (1.99-4.80)
  - Infection visits 1.74 (1.16-2.62)
  - Visits for CV or DM 1.49 (0.96-2.32)
  - Non-sarcoidosis ED 2.19 (1.46-3.30)

Ligon CB. Am J Med Sci 2011

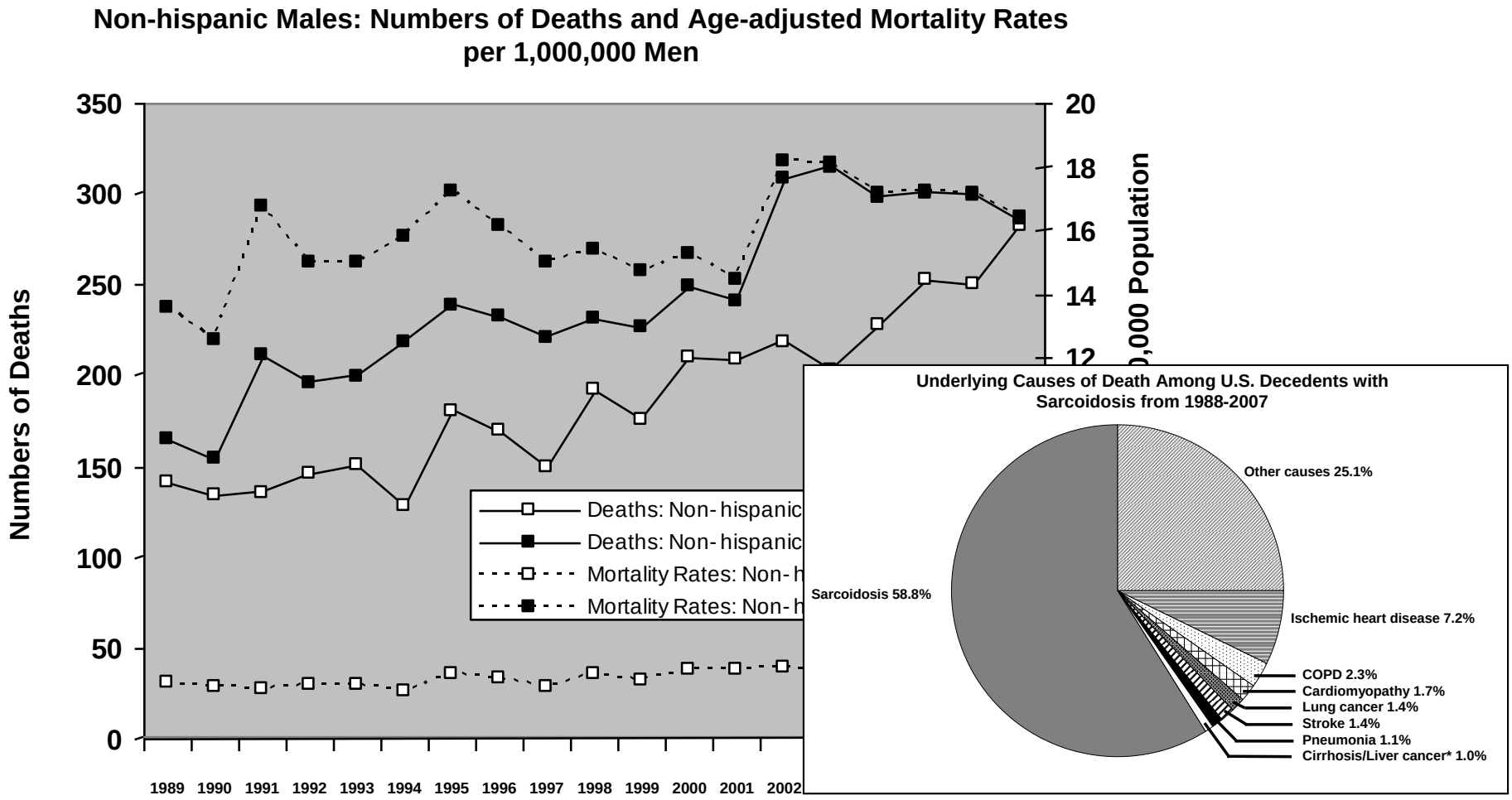
Rising number of sarcoidosis hospitalizations in the US





Gerke AK. BMC Pulm Med 2012

Rising sarcoidosis mortality in the US



Swigris JJ. AJRCCM 2011