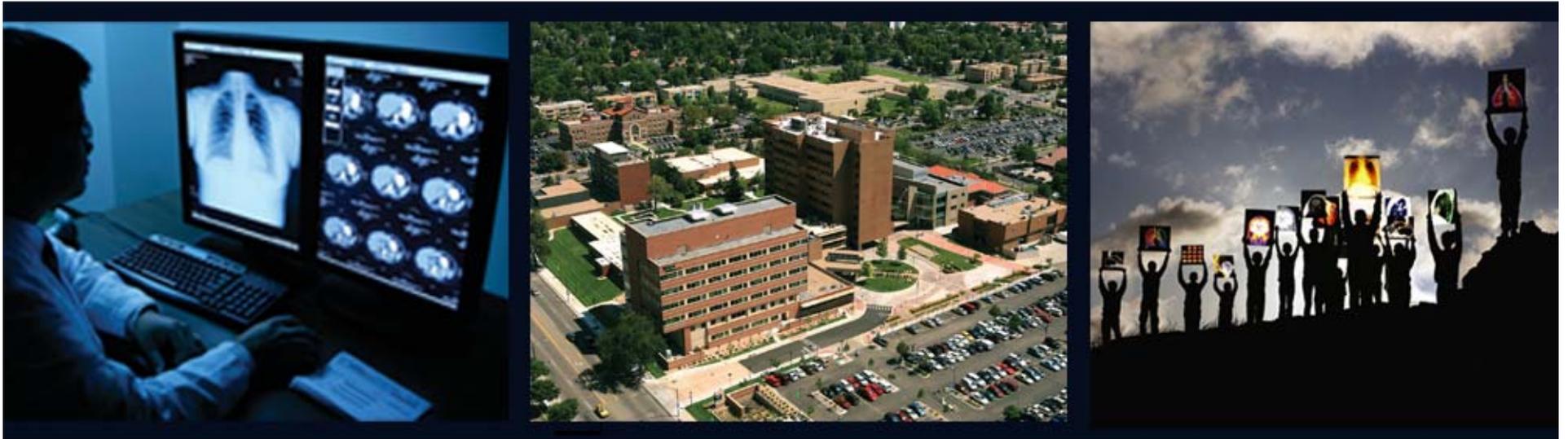


## **Update on the Detection and Clinical Management of Beryllium Health Effects**



**Peggy Mroz, MSPH**

**Division of Environmental Occupational  
Health Sciences**

- Review current diagnostic criteria
  - Evaluate the advantages and disadvantages of the BeLPT
- Discuss the prognosis and treatment for CBD
- Evaluate future directions and new assay development

## U.S. Department of Labor Criteria for CBD (Post-1993)

- Demonstration of beryllium specific immune response by abnormal BeLPT or BAL
- *AND* at least one of the following:
  - Lung biopsy demonstrating granulomatous inflammation consistent with CBD
  - CT scan showing changes in the lungs consistent with CBD
  - Pulmonary function or exercise tolerance test showing deficits consistent with CBD

# Beryllium Lymphocyte Proliferation Test (BeLPT)

- Detects beryllium-specific cell mediated immune response to help identify CBD at an early stage of the disease
- Differentiates CBD from lung disease of other etiology (sarcoidosis, COPD, hypersensitivity, pneumonitis)
- Increased sensitivity and specificity to diagnose BeS/CBD as compared to other tests/methods
  - Occupational Hx
  - CXR or CT scan
  - Spirometry

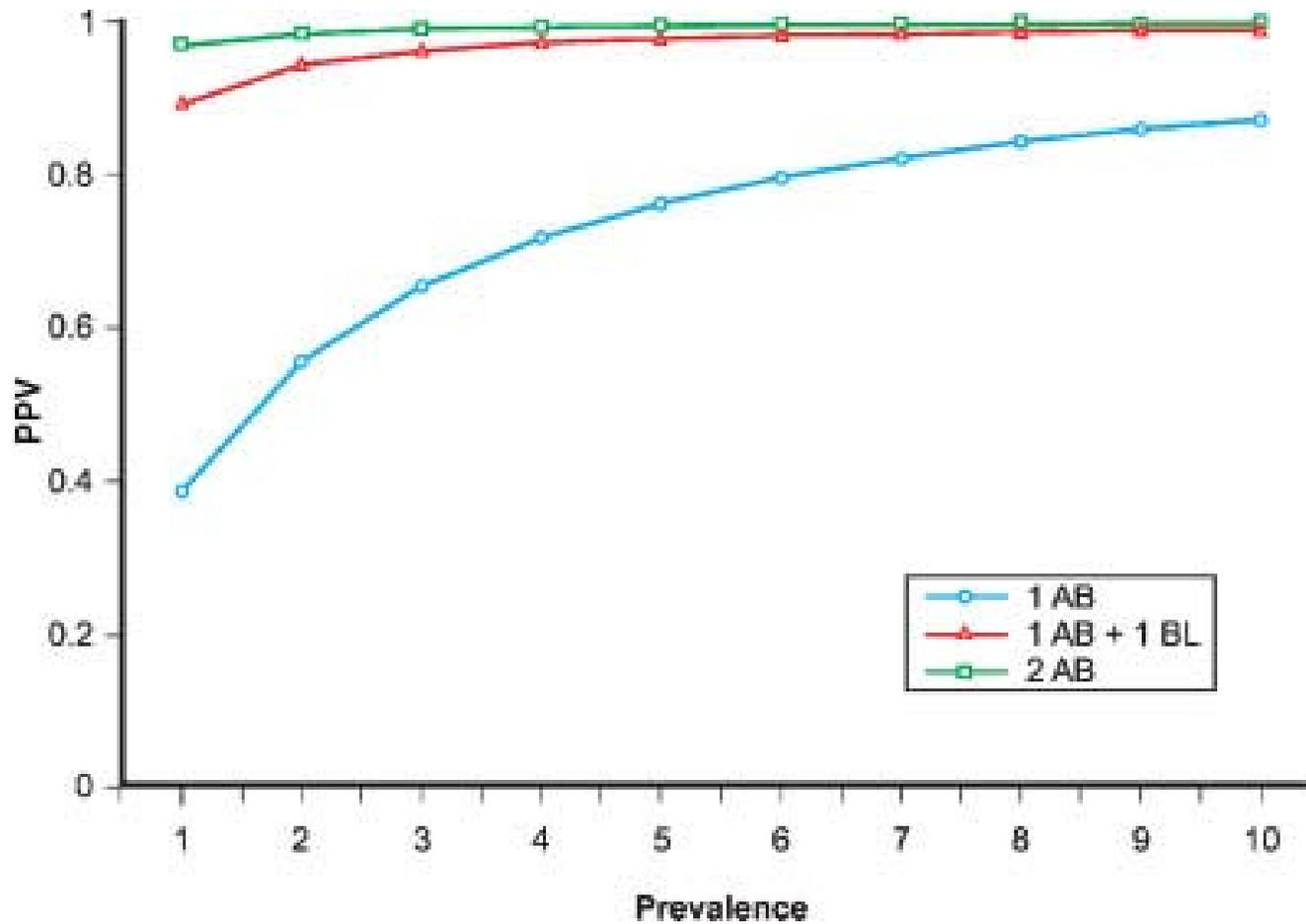
## **Advantages of the BeLPT**

- Simple blood test
- Highly specific
- Identifies sensitization to beryllium before progression to CBD

## **Disadvantages of the BeLPT**

- Does not distinguish between BeS and CBD
- Does not predict risk of progression to CBD or severity of disease
- Long TAT for results
- Not sensitive enough

# PPV of BeLPT by Prevalence



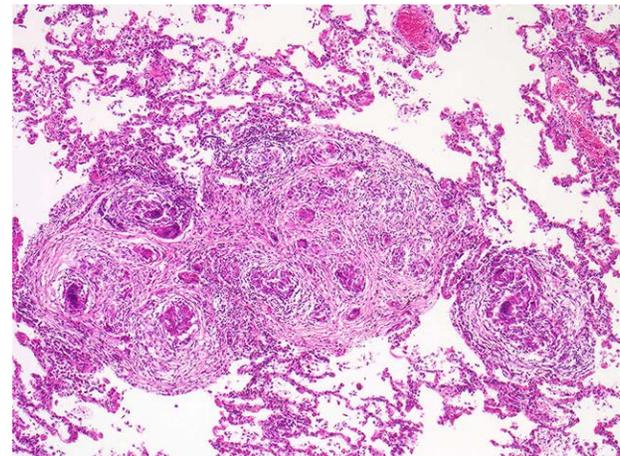
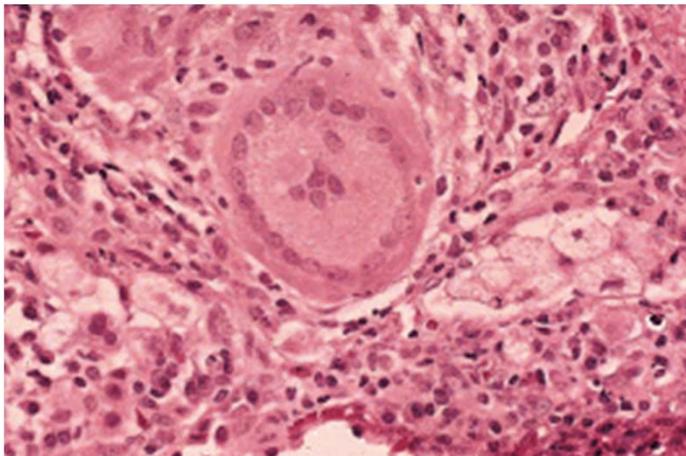
Middleton AJIM

# BeS: Evaluate for Progression to CBD

Currently recommend every 2 years follow up:  
6-8% progress from BeS to CBD

- History to determine if CBD/new symptoms
  - ✓ Asymptomatic
  - ✓ Respiratory symptoms: cough, shortness of breath, chest tightness
  - ✓ Systemic symptoms: fevers/night sweats, weight loss, muscle aches and joint pain
- Repeat clinical testing
  - ✓ PFTs, exercise test, chest Xray
  - ✓ Bronchoscopy with BAL and biopsy if indicated

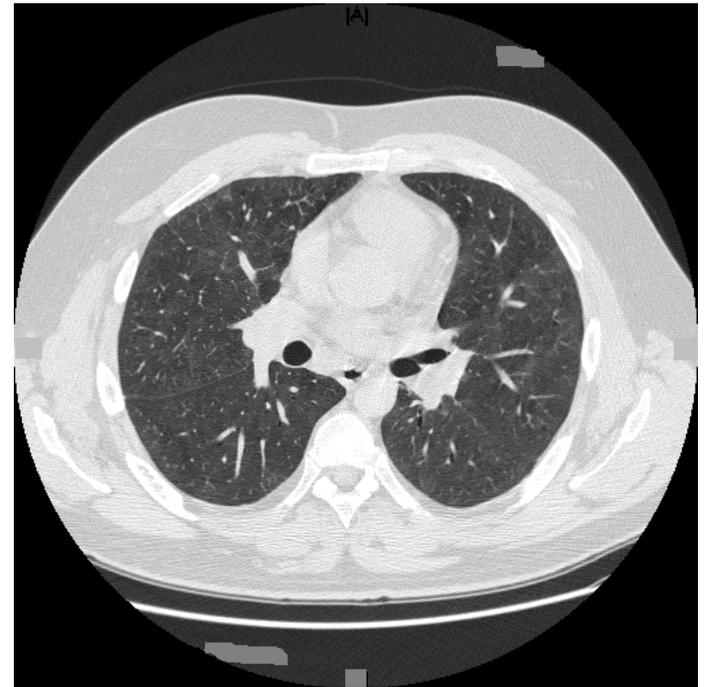
Presence of non-caseating granulomas with lung biopsy: Granulomas of CBD histopathologically indistinguishable from sarcoidosis granulomas



# High Resolution CT (HRCT)

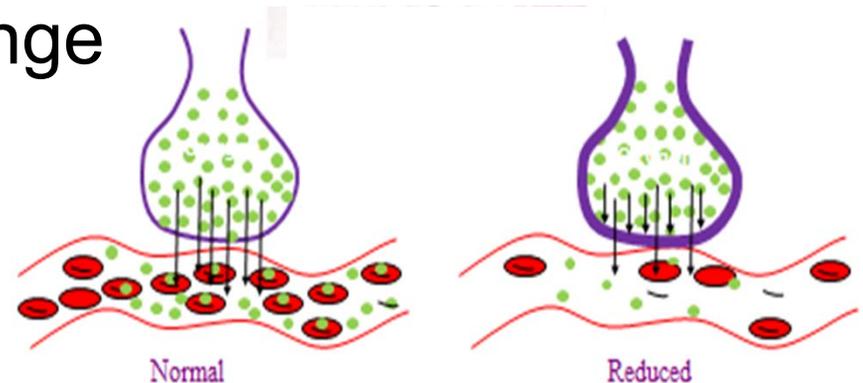
HRCT is negative in 25% of patients with documented CBD – more sensitive than CXR

- Ground glass opacities
- Parenchymal nodules
- Septal lines
- Hilar adenopathy
- Pleural thickening



# Pulmonary Physiology and CBD

- Early Stage Disease: obstructive physiology
  - Low FEV1, low FEV1/FVC ratio, may present with asthma-like symptoms
- Later Stage Disease: restrictive and mixed physiology
  - Low FVC, Low TLC
- Diffusing capacity (DLco): less sensitive than exercise gas exchange



# Exercise Tolerance Testing

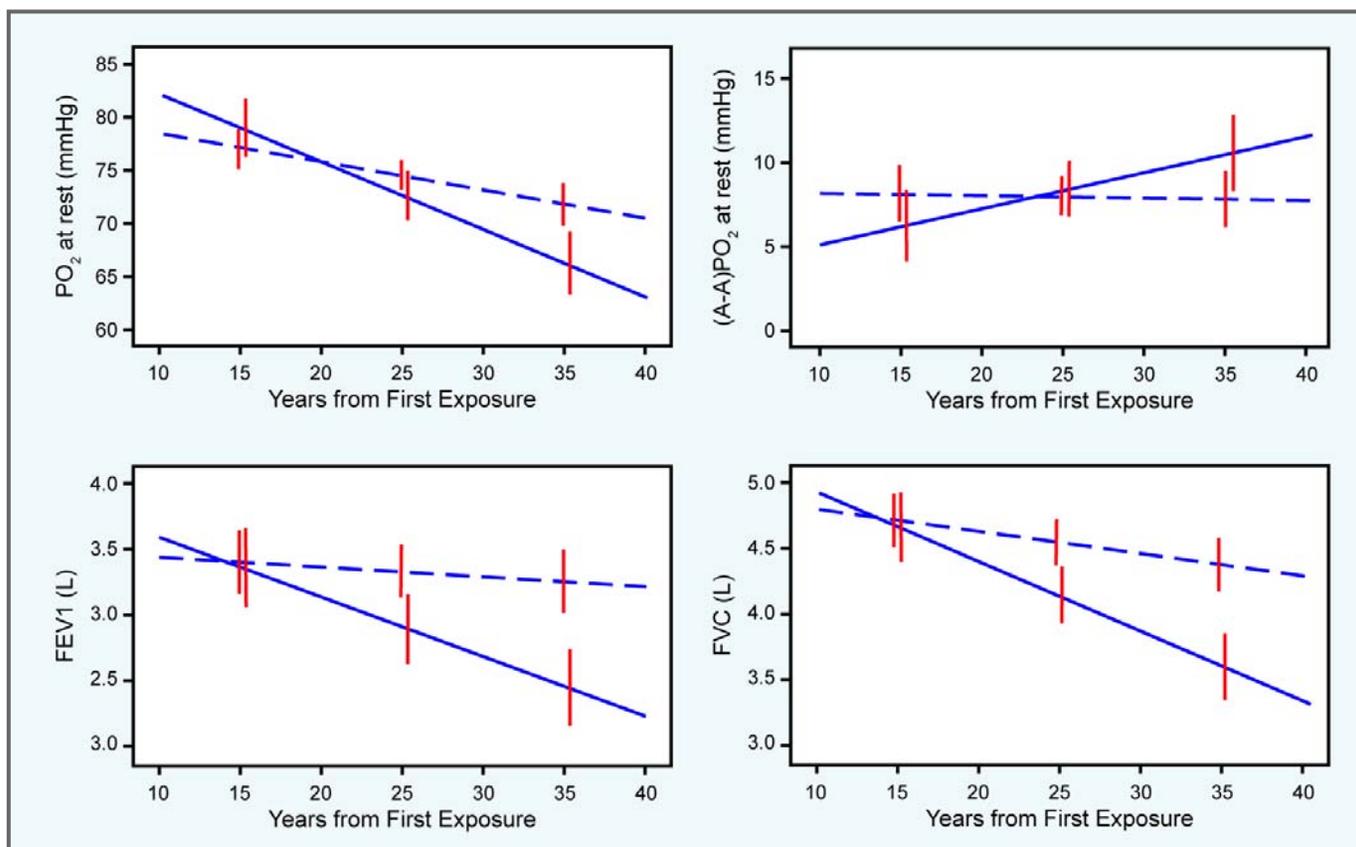
Most sensitive assessment of pulmonary  
physiology in CBD Pappas et al ARRD 1993

## Characteristics of patients with CBD

- Reduced exercise tolerance
- Abnormal gas exchange:
  - Decline in  $PaO_2$  or rise in A-a gradient at max exercise
  - Elevated  $V_d/V_t$
- More likely to be useful in surveillance identified cases



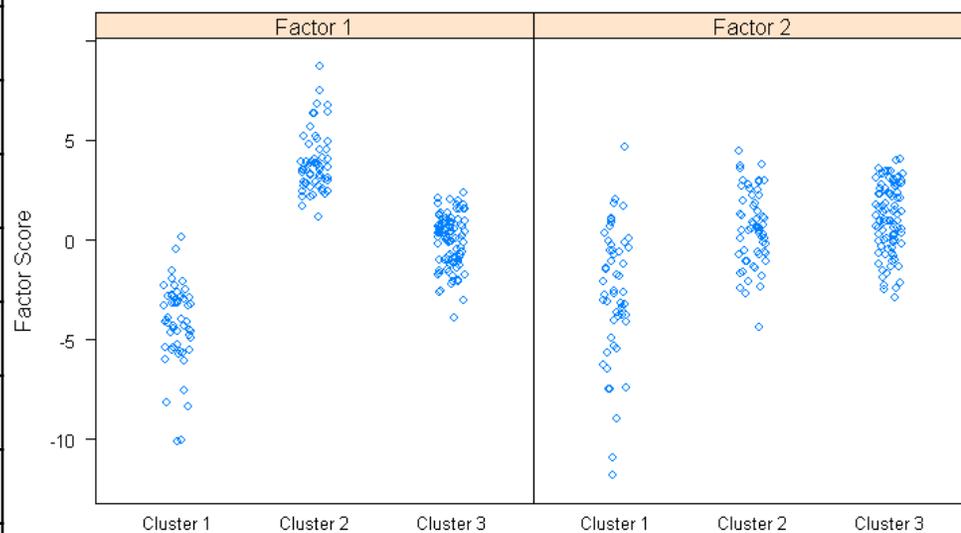
## Beryllium Lymphocyte Proliferation Test Surveillance Identifies Clinically Significant Beryllium Disease

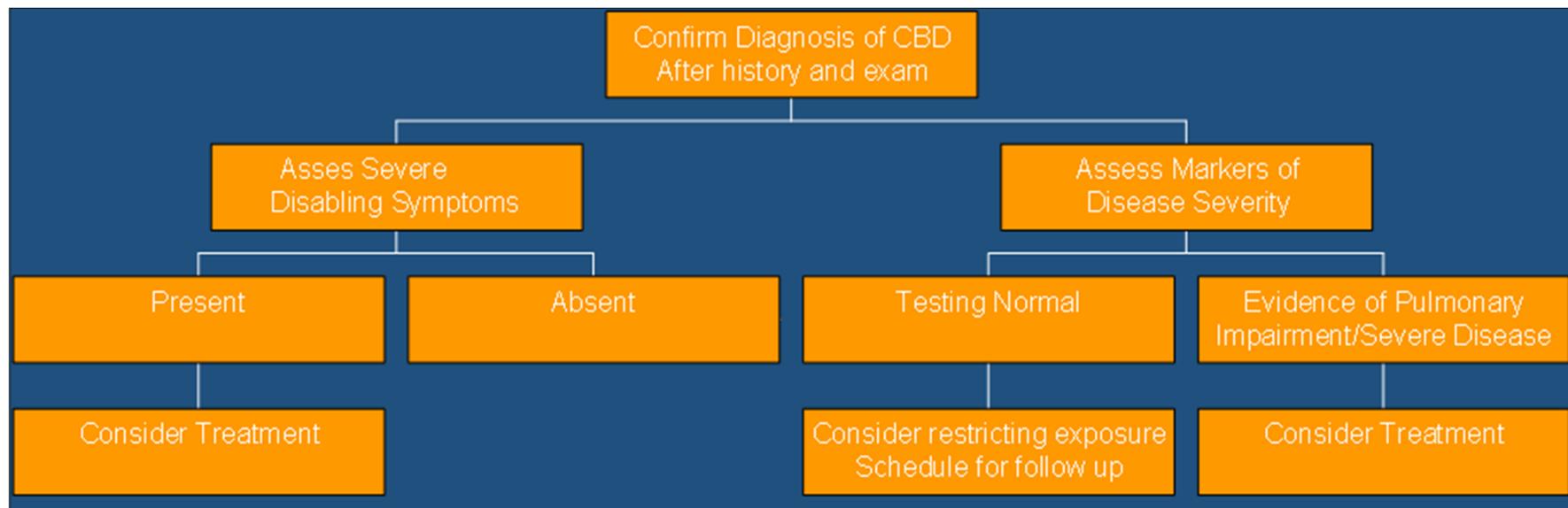


Lung Function Decline in CBD Machinists (AJIM Mroz, 2009)

# Descriptions of Severity in CBD

Variables	Covariance Parameter Estimates (Std Error)	P-value
FEV1 slope/intercept	-0.01(0.003)	<0.0001
FVC slope/intercept	-0.02(0.004)	<0.0001
TLC slope/intercept	-0.02(0.006)	0.008
DLCO slope/intercept	-2.9(0.47)	<0.0001
PaO <sub>2</sub> rest slope/intercept	-2.1(0.89)	0.018
PaO <sub>2</sub> max slope/intercept	-3.8(1.4)	0.05
PA-aO <sub>2</sub> rest slope/intercept	-1.5(0.74)	0.0013
PA-aO <sub>2</sub> max slope/intercept	-6.6(2.0)	0.0002
VO <sub>2</sub> max slope/intercept	-0.008(0.002)	0.04
WLM slope/interest	-76.5(15.6)	0.0014





- The course of CBD is **variable**
- Historical mortality rates range from 5-38%
- Early detection and therapy improves the outcome
- Once CBD is clinically apparent, it appears to progress
- A complete cure with or without treatment is rare and therapy is aimed at **controlling the disease**
- Therapy includes immunosuppressive agents, such as prednisone and methotrexate and supportive measures including the use of oxygen, antibiotics
- Removal from work is recommended

## **Indications for use:**

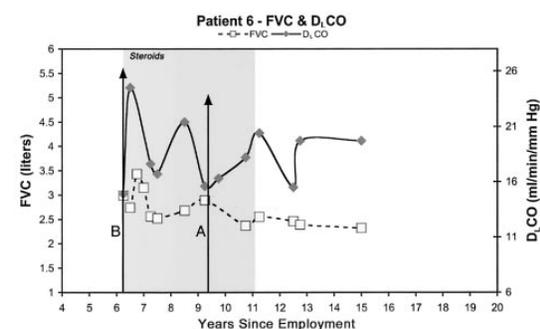
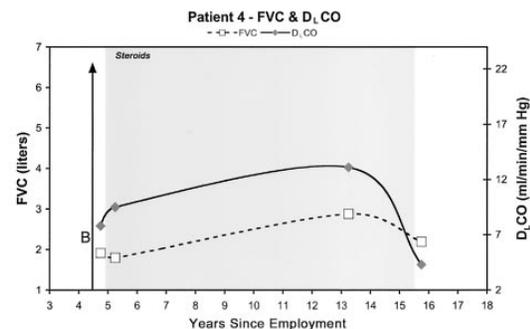
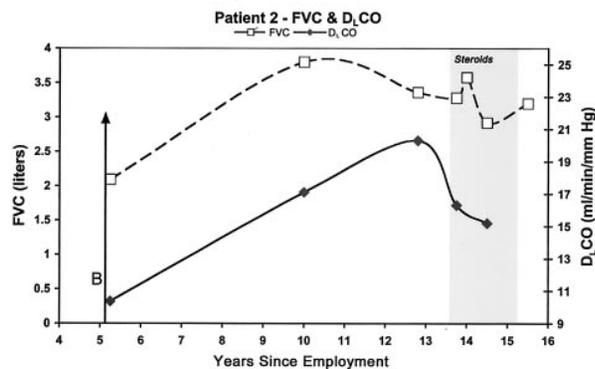
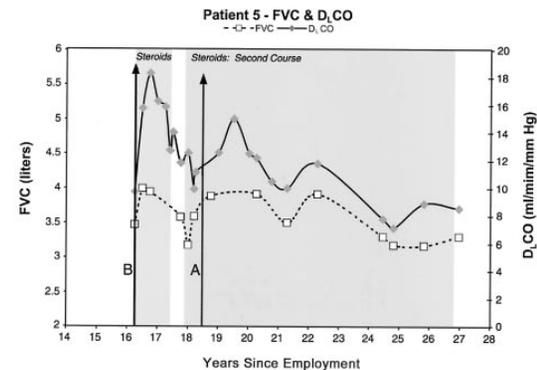
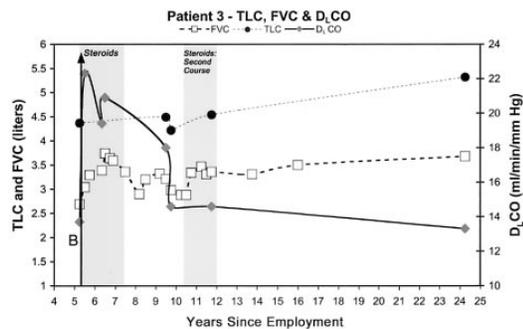
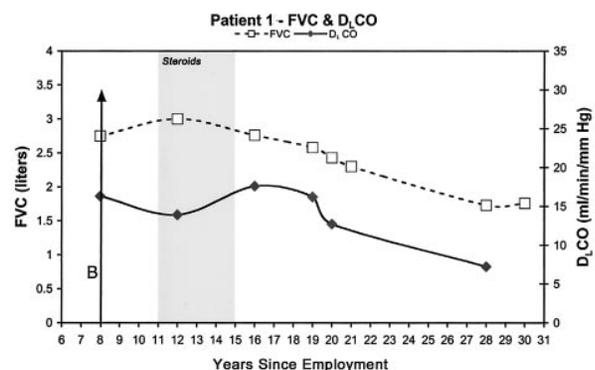
- Severe symptoms
- Impairment in the lungs ability to transfer oxygen to blood
- Worsening of exercise capacity or pulmonary function tests
- Evidence of stress and strain on the heart and vessels in the lungs

## **Treatment approach:**

- 40mg/d or every other day
- Add bisphosphonate daily
- Continue prednisone for at least a few months
- Taper to lowest alternate day dose possible, to maintain symptomatic and radiographic improvement
- Follow objective markers

Early identification of CBD patients who are likely to progress to severe disease will modify treatment regimen

- Timing of steroid initiation is key to good prognosis



(Sood, et al., Chest, 2004)

- Weigh side effects against potential benefit in treating CBD.
- Side effects: related to **dose** and **duration**.
- Monitoring for Side Effects of Prednisone

## Potential Side Effects:

- Weight gain
- Changes in skin
- Osteoporosis
- Psychiatric problems
- Cataracts
- Peptic ulcers or stomach upset
- Increase in high blood pressure
- Worsening of diabetes

- Indications: Steroid sparing, not steroid replacing
- Side effects:
  - Decreased white blood cell counts and increased risk of infections
  - Liver function abnormalities
  - Lung inflammation
- Monitoring for side effects:
  - Blood work checked frequently for the above abnormalities along with respiratory symptoms

# Studies of other Therapies



## Infliximab

- First RDBPCT of the drug infliximab in CBD.
- Infliximab altered the pulmonary immune response.
- Improvements in quality of life with treatment.
- Patients with more severe gas exchange demonstrate clinical response

Maier LA, et al, 2012

## Inhaled steroids

- Retrospective study
- Compared those treated with ICS to untreated
- No change in lung function over time for those treated suggesting stabilization
- Improvement in symptoms of cough

Ferguson submitted

# Other Forms of Therapy

- Supportive measures
  - ✓ Oxygen
  - ✓ Diuretics
  - ✓ Bronchodilators
  - ✓ Antibiotics for infections
  - ✓ Medications for side effects of primary therapy
  - ✓ Psychological and social counseling
- Health improvement measures
  - ✓ Smoking Cessation
  - ✓ Physical activity/therapy/Rehab
  - ✓ Weight Control
- Lung transplantation

## Goals

- 1) Develop reliable diagnostic tools faster, less expensive and easier for industry to protect employees
- 2) Eliminate the need for BAL and lung biopsy to diagnose disease

## New Tests being evaluated

- Blood test that can distinguish between BeS and CBD
  - ELISpot
  - Other Cytokine Assays
- ?Genetic Markers
- Other Biomarkers

Detects cytokine secretion on a cell-by-cell basis

Distinguishes between BeS and CBD

## Advantages:

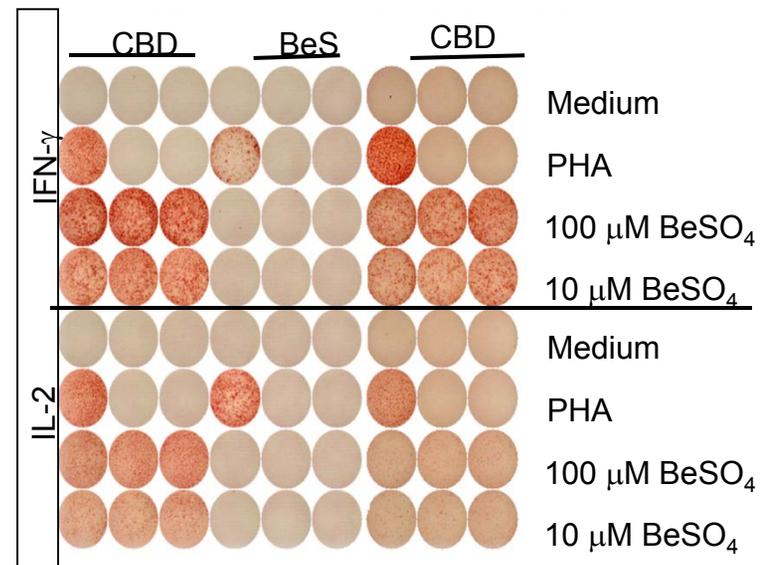
Does not rely on proliferation which can be negatively impacted by time, environment, technician error

Shorter TAT for results (24 hrs)

No radioactivity

## Disadvantages:

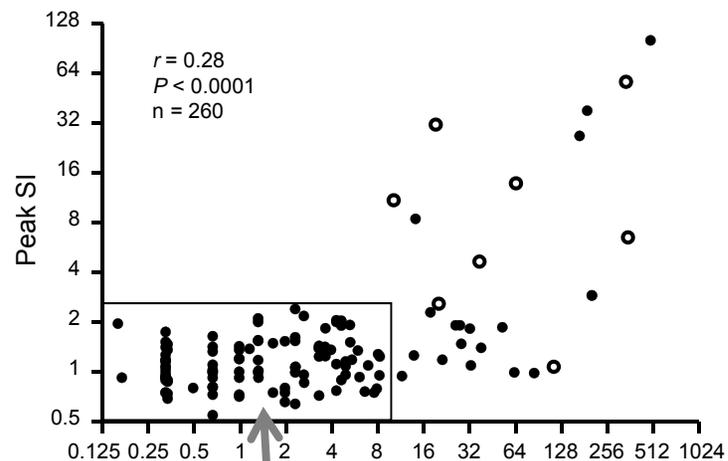
Requires ELISpot reader



# Be-ELISPOT in Diagnosis

Martin JACI 2011

- Follow up study compared to BeLPT in med surveillance
- Longitudinal study to determine if can differentiate CBD from BeS- some (but not all)
- Positive Be-ELISPOT with normal BeLPT



Normal BeLPT and ELISPOT

Open circles CBD

# Beryllium Whole Blood Assay

- Early stages of research
- Detect cytokines from Be stimulated cells
- May differentiate BeS and CBD
- Could potentially be used to determine disease severity

## Advantages:

Simple, assay

Shorter TAT for results (48 hours)

No radioactivity

## Disadvantages:

May need processing within hours

Uses Be

# Genetic Susceptibility and CBD

CBD is a multigenetic disease

- Immune response genes, such as HLA
- Disease development or progression genes

Susceptibility factors: HLADPB1 Glu69

Progression factors: ?

Developing CBD requires a gene and environment interaction

**Current Markers are not for clinical use**

# The Role of Genetics & Exposure in CBD

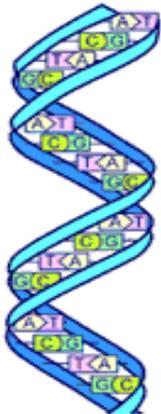


Illustration by US DOE available under public domain  
from [Wikimedia Commons](https://commons.wikimedia.org/wiki/File:DNA_Double_Helix.jpg)

**Your Genes**

+

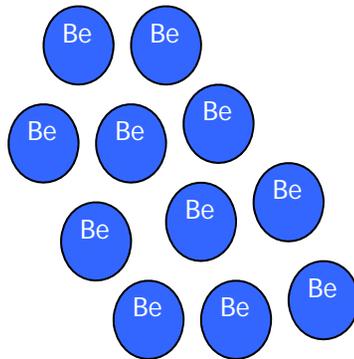


Illustration by National Jewish Health

**Beryllium  
Exposure**



No immune  
response



Immune  
response

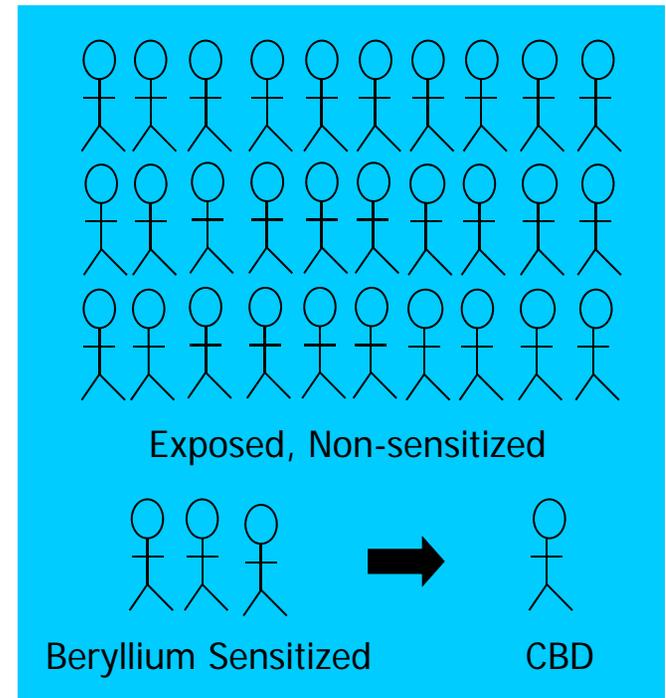
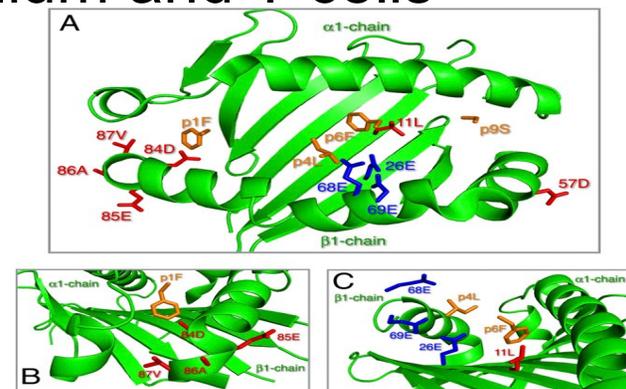


Illustration by National Jewish Health

## Chronic Beryllium Disease, HLA-DPB1, and the DP Peptide Binding

Silveira LJ, et al., 2012

- Examined the Glu69 genetic marker for beryllium disease
- Found that some variants of the marker carried more risk for CBD than others
- Helps us to understand how beryllium and T-cells interact to cause disease



# Positive Predictive Value of Glu69

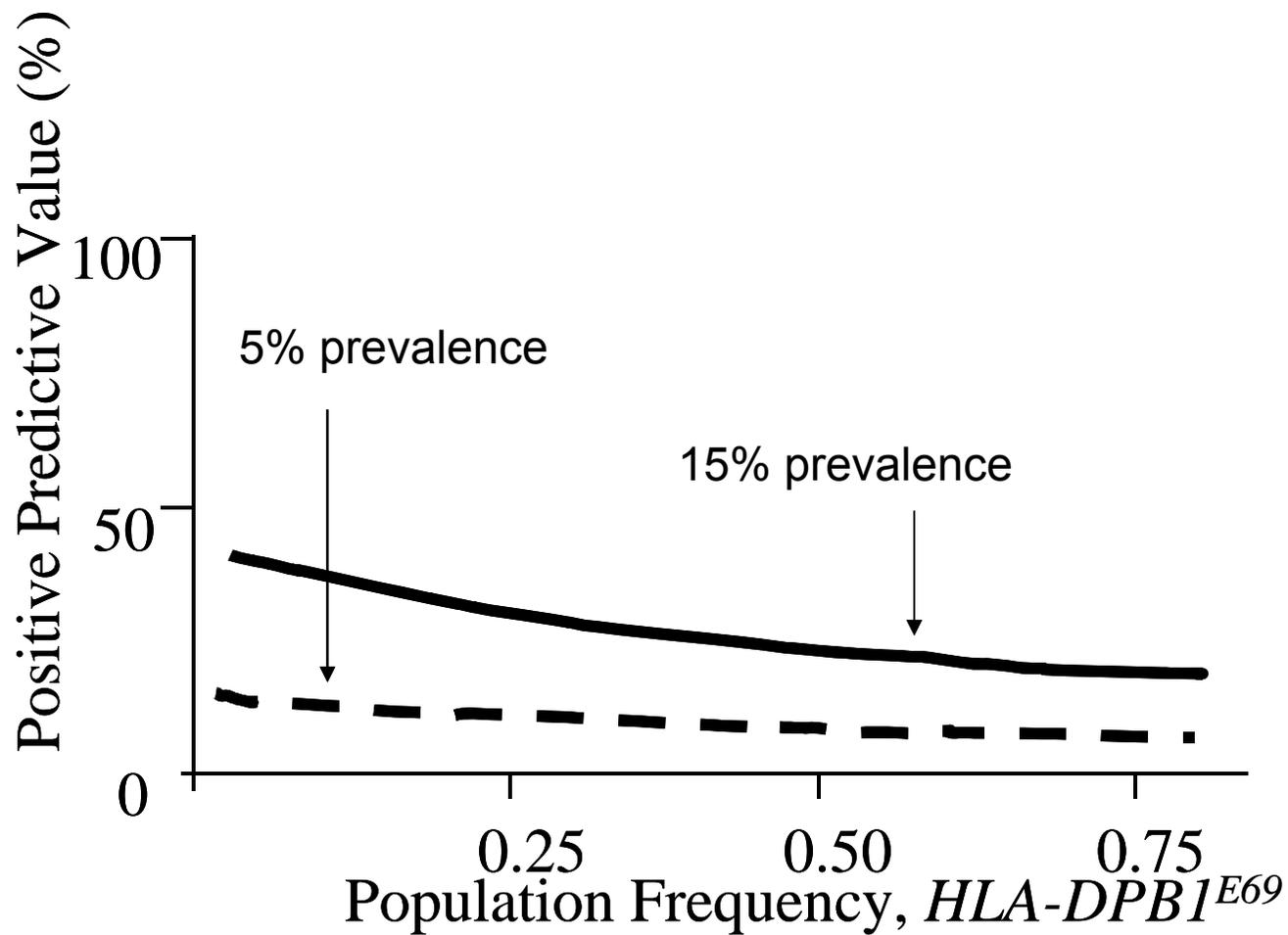
Prevalence 10%  
Sensitivity 80%

	CBD +	CBD -
Glu69 +	80	360
Glu69 -	20	540
	100	900
	$80/440 = 18\%$	

Prevalence 5%  
Sensitivity 80%

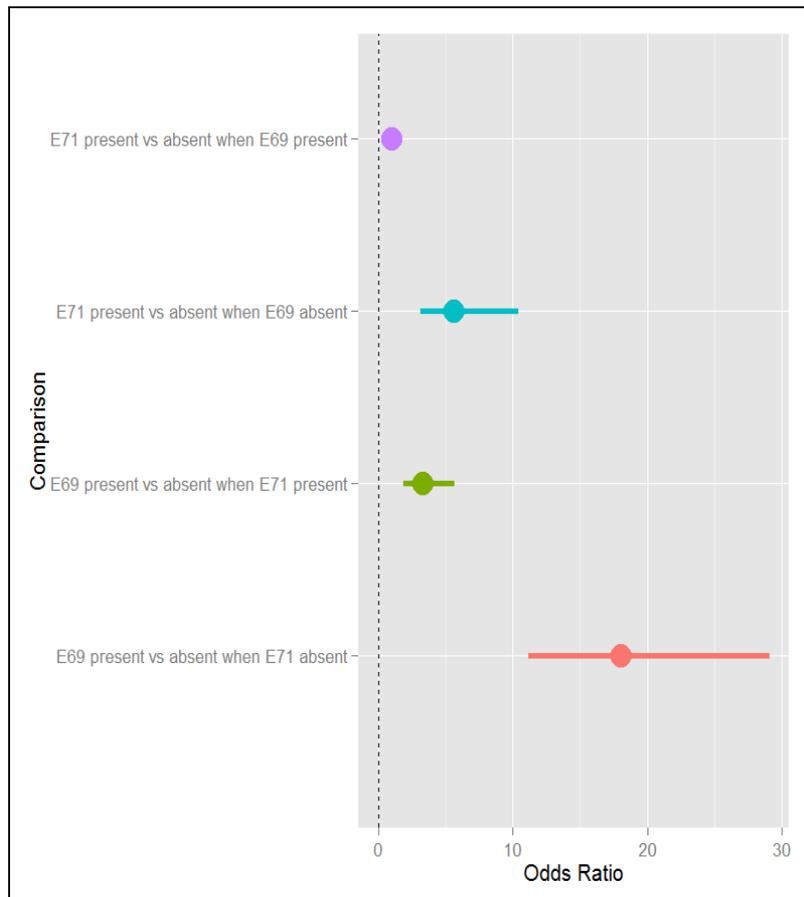
	CBD +	CBD -
Glu69 +	40	380
Glu69 -	10	570
	50	950
	$40/420 = 10\%$	

# PPV for Glu69

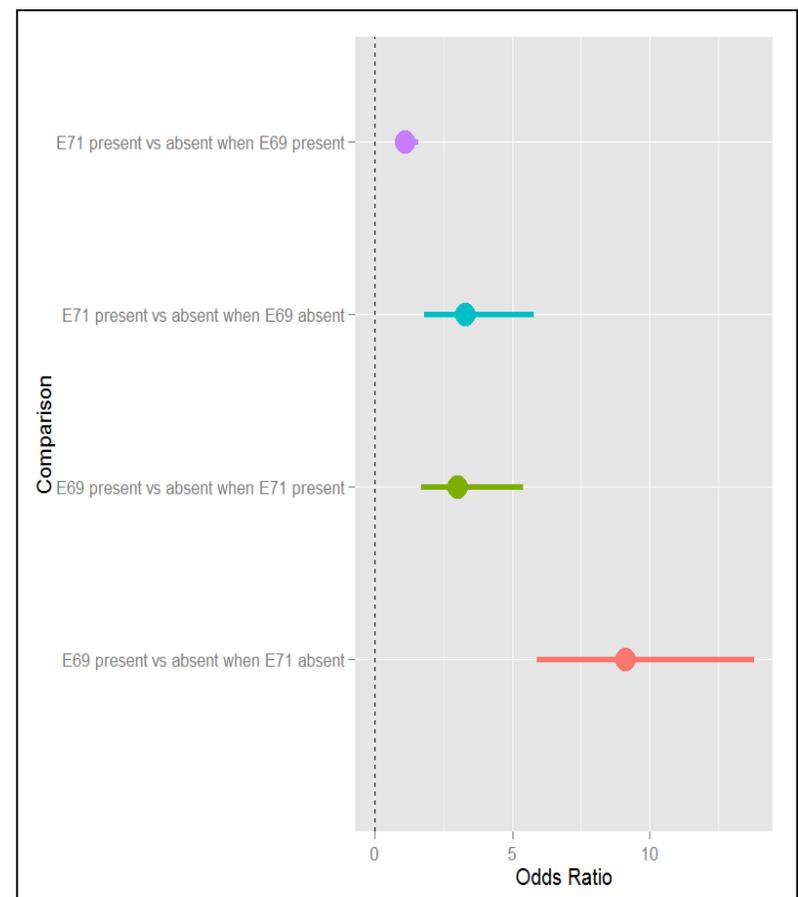


# The Role of Glu71 in BeS and CBD

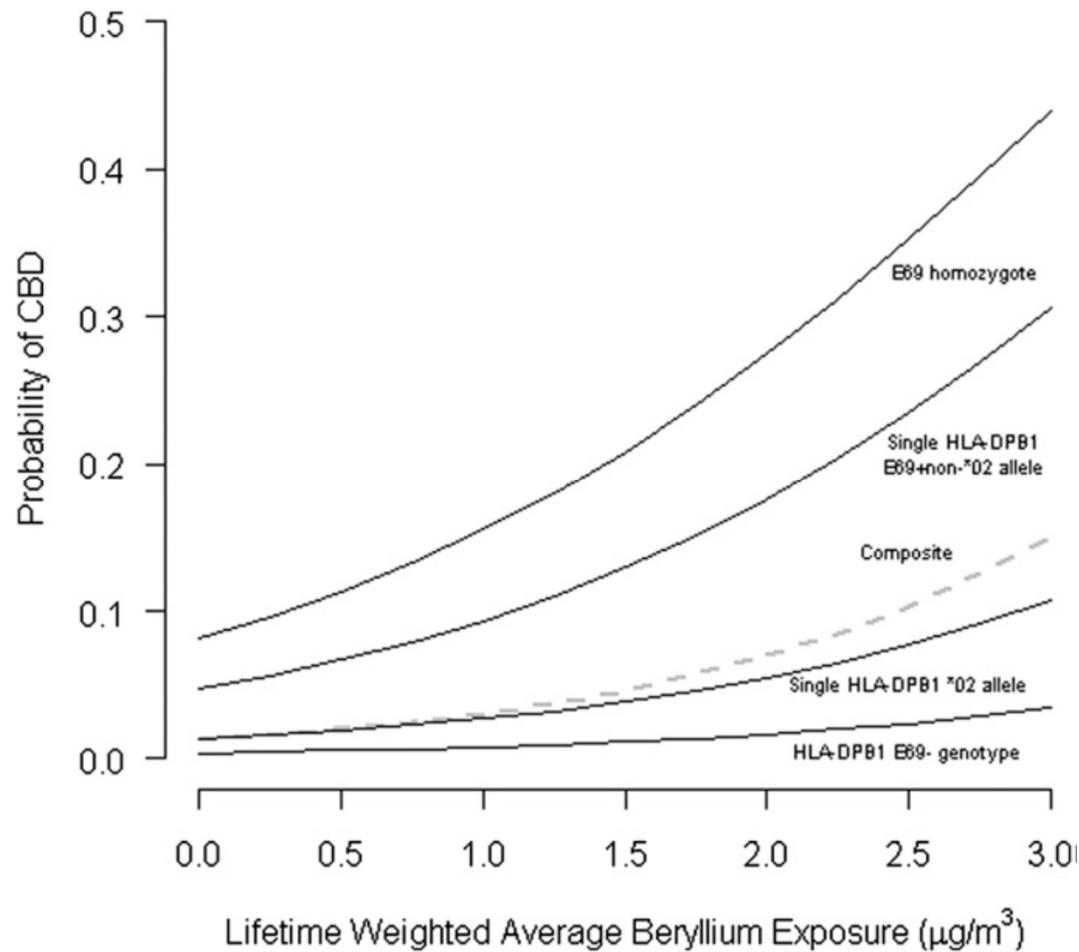
CBD vs. Control

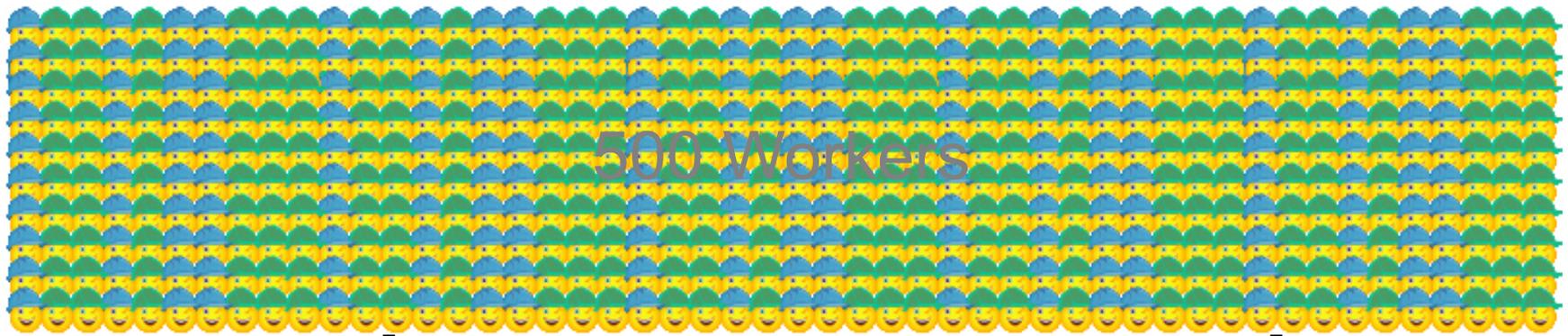


BeS vs. Control



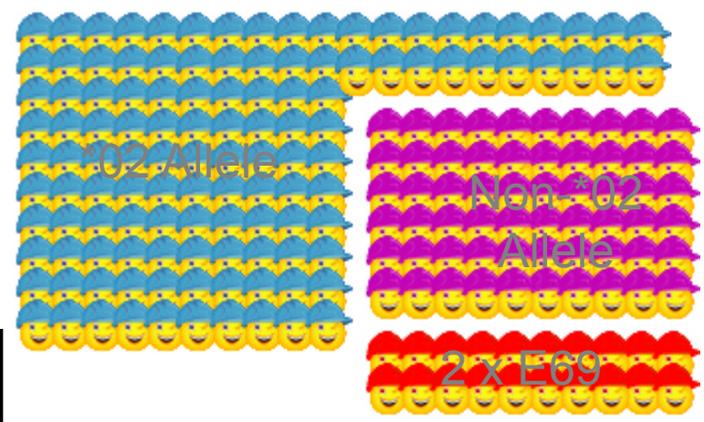
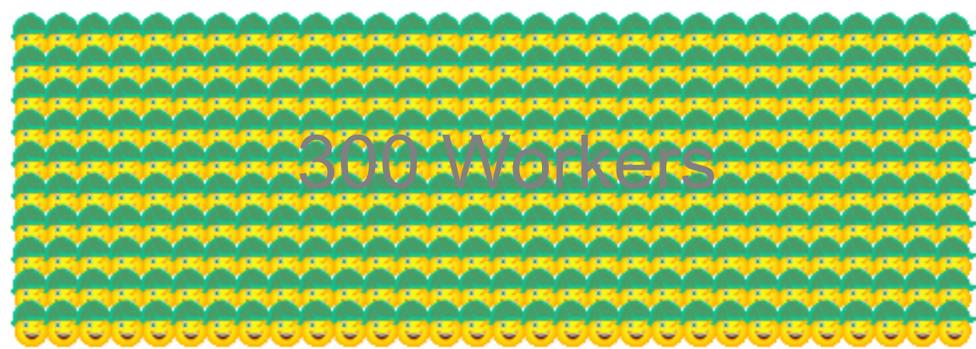
# The Role of Genetics and Exposure in CBD





E69-

E69+



2% BeS

0.3%

2.5%

6.7%

10%



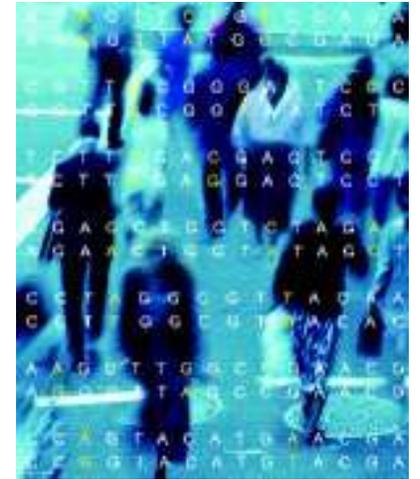


# GINA: Genetic Information Nondiscrimination Act

The use of genetic testing to discriminate against individuals is prohibited by insurance companies and employers

- Insurers cannot reduce/deny coverage or invoke pre-existing condition exclusions based on genetics (Title I)
- Employers cannot make hiring, firing or promotion employment decisions based on genetics, enforced by EEOC (Title II)
- Neither can request or demand a genetic test or results

- Do not know longitudinal PPV
- Difficulty in interpreting PPV, test results
- Current PPV low
- Negative test does not equal no risk
- Workers had to make decision about work-shift of responsibility from employer
- No involvement of workers, union in program
- ?Protect confidentiality



# Worker Knowledge, Beliefs & Attitudes

Silver et al AJIM 2011

- Focus groups re: Be and Glu69
- Knowledge deficit: genotoxicity vs. heritability
- Would want independent, financial separate testing
- Desire for autonomy- selves and family
- Desire for confidentiality and decision for disclosure
- Concern about misuse of information
- “Superman Syndrome” & lack of exp controls

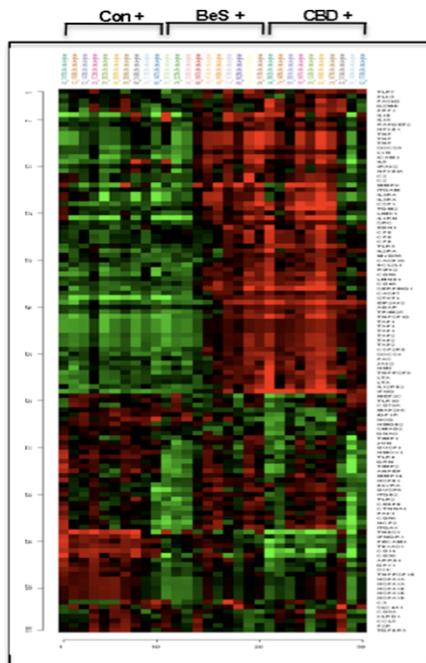
# Genetic Workplace Testing

- Legal and policy lagging behind science
- Genetic discrimination
- Shift of responsibility from employer to employee
- Double edged sword: prevent disease and threaten autonomy, loss of insurance, employment, etc
- Exposure may be ignored
- Other factors affect disease
- Is prophylaxis or treatment an option
- Others: privacy, psychological impact

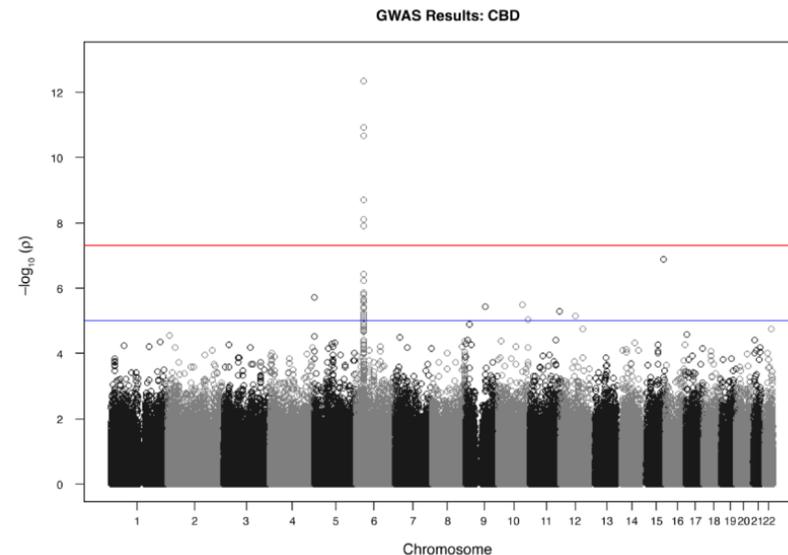
# Other Ethical Issues to Consider

- Education is needed to help healthcare providers and workers understand genetic testing
- Individuals receiving test results need to be counseled regarding the implications of the results. Usually a genetic test  $\neq$  disease
- The public needs to be prepared to be able to make decisions about risk and risk modification
- Many other questions to address as a society...

- Examine other ways to define severity, e.g. factor analysis
- Clusters may be used with high dimensional data: GWAS or microarray data



**Figure 1. Heat map representing expression profiles of Be-stimulated control, CBD vs. BeS determined by microarray analysis. Red indicates increased expression, while blue indicates decreased expression relative to the non-failing population mean.**



- BeLPT is cornerstone of BeS and CBD diagnosis
- Need bronchoscopy or other testing to define CBD
- ELISpot or other tests may be able to differentiate CBD from BeS
- CBD progresses to severe disease in some
- Treatment options: Prednisone Risks vs Benefits
- Limiting exposure medically prudent: Unclear if this changes the long term outcome of BeS or CBD
- Genetic Risks for BeS and CBD but not appropriate as Biomarkers

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# Other Possible Treatment Options

Therapies that have not been formally studied:

- Inhaled steroids
- Other immunosuppressive agents:
  - Cytoxan or cyclophosphamide
  - Immuran
- Complementary or alternative therapies

Therapies in the research stage

- Immunotherapeutics