

Three Borderline Beryllium Lymphocyte Proliferation Tests (BeLPTs) Predicts Beryllium Sensitization

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Overview

- BeLPT overview
- Significance of the borderline (BL) BeLPT
- Algorithms that diagnose beryllium sensitization (BeS)
- Future directions

Importance of Detecting Immune Sensitization to Beryllium (BeS)

- Identify workers who are at risk for chronic beryllium disease.
 - Earlier identification and treatment of disease
 - Counseling to minimize ongoing exposure
- Suggests that exposure controls in the workplace may need to be improved.
- Other workers in the same area or in similar jobs might also be at risk.

BeLPT: Detects Immune Cell Response

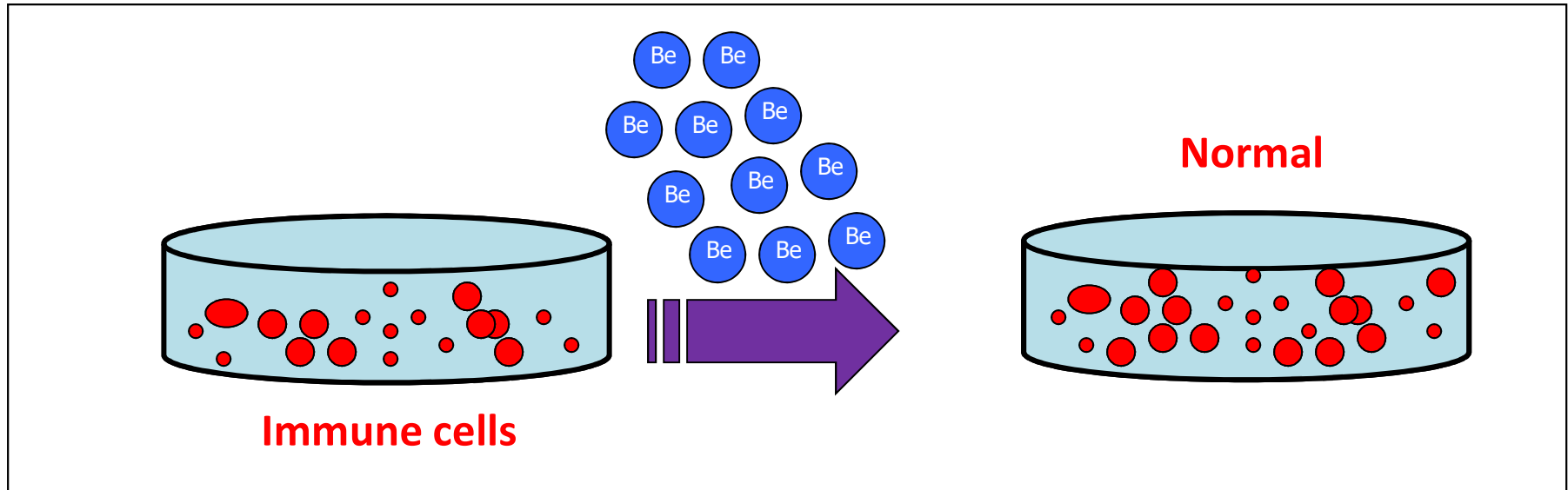


Illustration by National Jewish Health

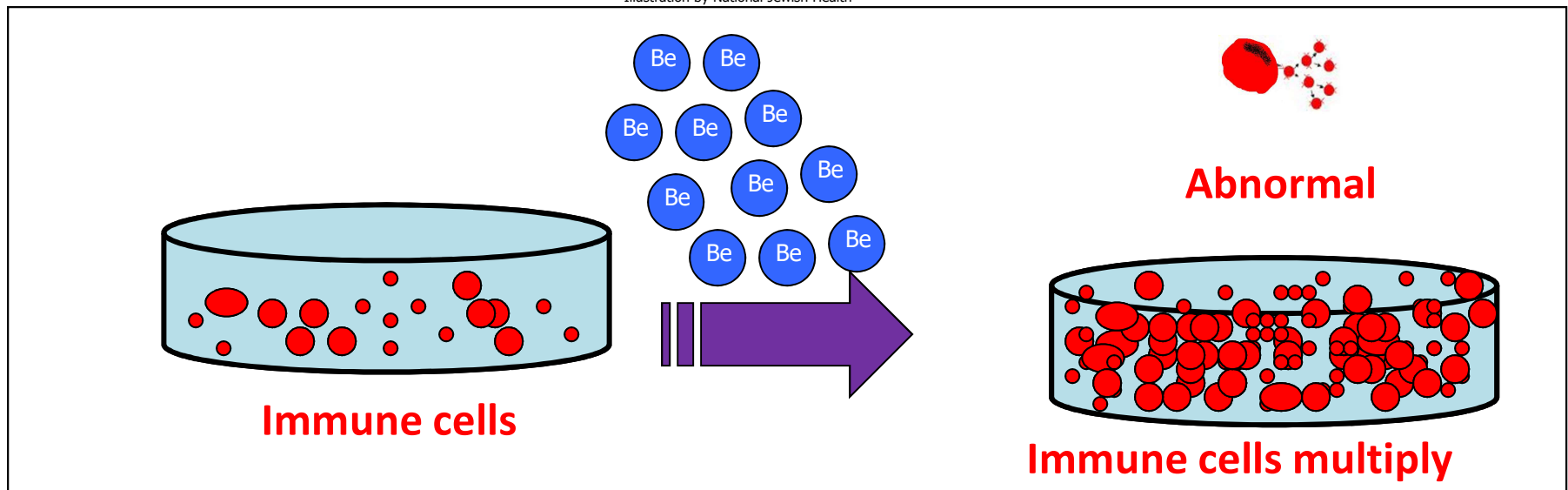
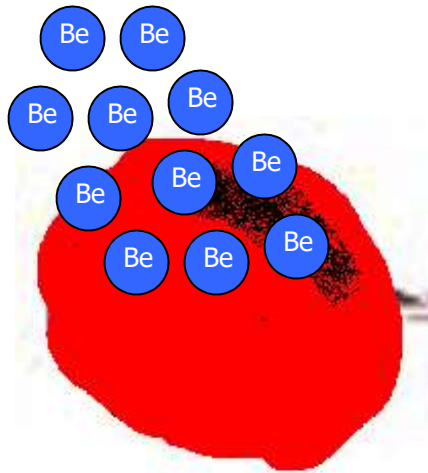
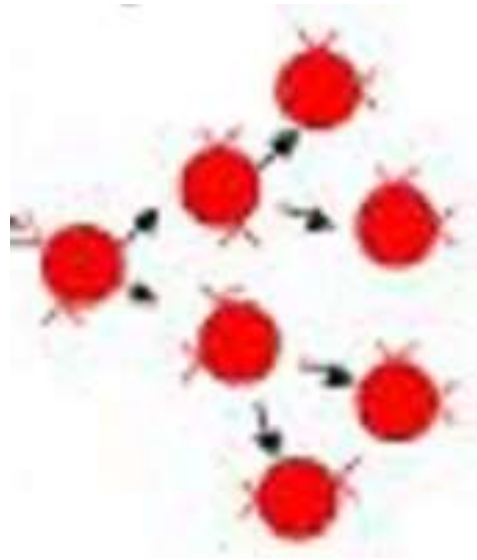


Illustration by National Jewish Health

Beryllium Specific Immune Response



Each of these newly formed immune cells is proliferating in response to the beryllium antigen

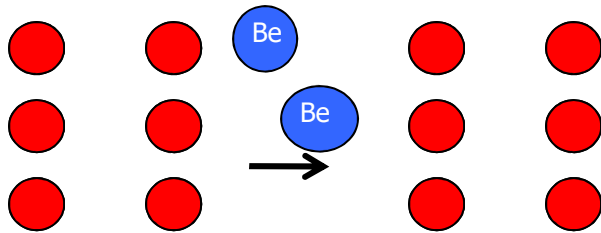


This can happen in the blood and the lung

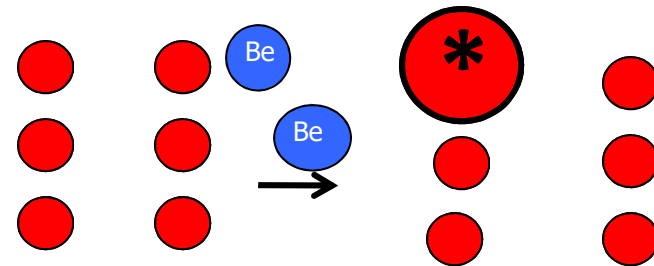
**MOST EXPOSED
INDIVIDUALS
NEVER MOUNT
THIS SPECIFIC
IMMUNE
RESPONSE**

BeLPT Results

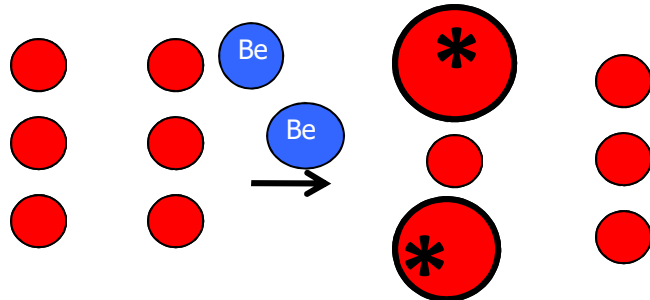
Normal (Negative)



Borderline



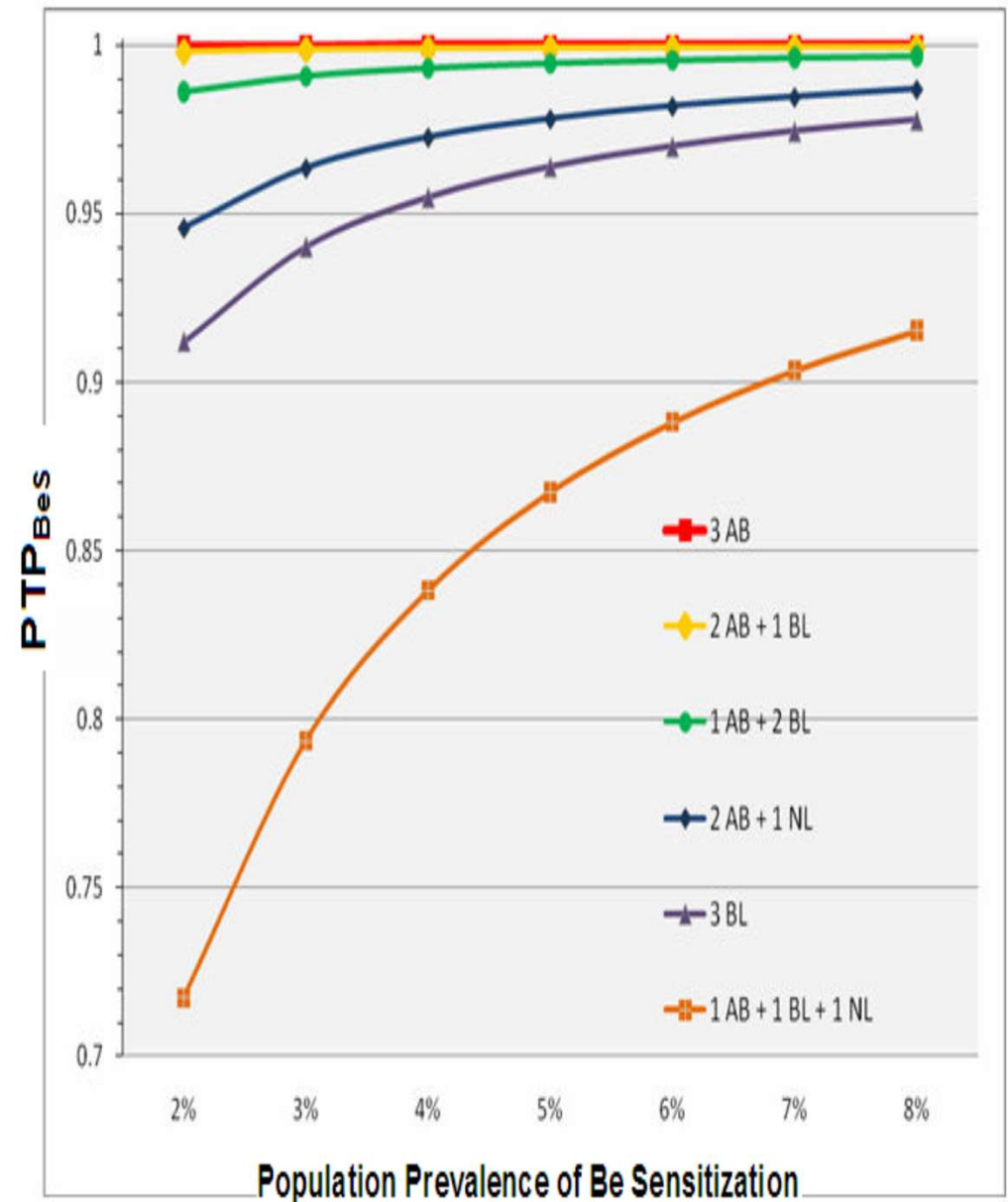
Abnormal (Positive)



- Not normal or abnormal
- The test needs to be repeated.
- The most common result of the repeat test is normal.

Predictive Value of BL BeLPT

- 1 AB + 1 BL
- 3 BLs
 - Predictive value approaches 2 AB
 - Prevalence ≥ 2 -3%



Does CBD Develop In Those With Repeated Borderline BeLPTs?

Mayer AS, Mroz MM, Van Dyke MV, Maier, LA
Scientific Abstract Poster American Thoracic Society Annual Meeting 2012

The Beryllium Lymphocyte Proliferation Test (BeLPT) identified BeS

- **BeS:** 2 AB BeLPTs or AB bronchoalveolar lavage (BAL) BeLPT
- **Abnormal BeLPT (AB):** ≥ 2 of 6 stimulation indices are elevated.
- **Borderline BeLPT (BL):** 1 elevated stimulation index.

A recent study suggested that **3 BL BeLPTs** could predict BeS based on modeling (Middleton et. al. 2011)

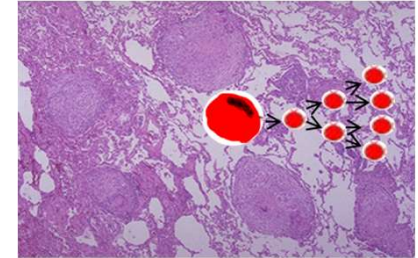
Hypothesis: Repeated BL BeLPTs, in the absence of an AB test, can predict CBD.

Methods

- Medical record review: Workers evaluated in our clinic for possible CBD based on repeated BL BeLPT results without any AB results.
- The diagnosis of CBD was confirmed by BeS (AB BAL BeLPT) and granulomas on biopsy.
- The diagnosis of granulomatous lung disease (GLD) was established by granulomas on biopsy, no AB BeLPTs, and no evidence of other cause of GLD.
- An estimate of beryllium exposure (high, medium, low) was provided by an industrial hygienist.
- Demographics, PFTs, radiographic findings, BeLPT results, estimate of exposure, and final diagnosis were reviewed to characterize this population of beryllium-exposed workers.

Results

We identified 10 workers with ≥ 2 BL BeLPTs who were evaluated for CBD



Results of Diagnostic Evaluation and Diagnosis

Number of BL BeLPTs	Respiratory Symptoms	Radiographic findings consistent with CBD	Abnormal BeLPT Results	Granulomas on Biopsy	Diagnosis
3	-	-	BAL	+	CBD
2	+	+	BAL	+	CBD
3	+	-	Blood	-	BeS
3	-	-	BAL	-	BeS
3	+	+	-	+	GLD
3	+	-	-	+	GLD
3	+	-	-	-	Be exposed
3	+	-	-	-	Be exposed
3	+	-	-	-	Be exposed
2	+	-	-	-	Be exposed

Results

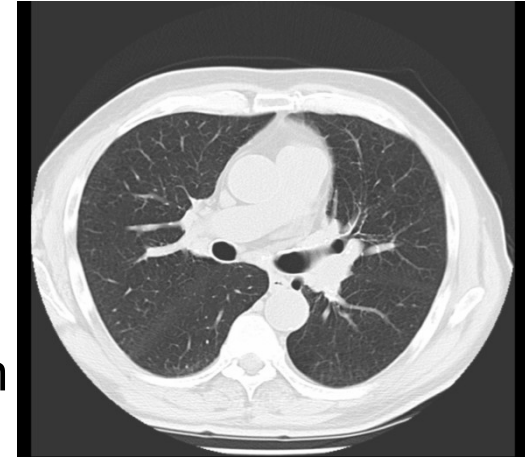


Demographics and Estimated Exposure by Diagnosis Group

Diagnosis	Age (median (range))	Gender	Smoking Status	Steroid use	Estimated amount of exposure
CBD (n=2)	60 years (56-63)	Male (n=2)	Never (n=1) Current (n=1)	None (n=2)	High (n=1) Low (n=1)
BeS (n=2)	66 years (48-83)	Male (n=1) Female (n=1)	Never (n=2)	Inhaled (n=1) None (n=1)	Medium (n=2)
GLD (n=2)	54 years (45-63)	Male (n=2)	Never (n=1) Former (n=1)	None (n=2)	High (n=1) Low (n=1)
Negative evaluation (n=4)	47 years (30-55)	Male (n=3) Female (n=1)	Never (n=2) Former (n=2)	Inhaled (n=1) None (n=3)	High (n=1) Low (n=3)

Results

Radiographic Findings and Pulmonary Function Test Results at Diagnosis



Diagnosis	Radiographic findings	TLC (median (range), % pred)	FEV1 (median (range), % pred)	DLCO (median (range), % pred)
CBD (n=2)	Abnormal (n=1)* Normal (n=1)	113% (113)	94% (93-94)	88% (83-92)
BeS (n=2)	Normal (n=2)	119% (99-138)	84% (81-85)	83% (78-88)
Sarcoidosis (n=2)	Abnormal (n=1)* Normal (n=1)	105% (103-106)	95% (91-98)	88% (83-92)
Negative evaluation (n=4)	Evidence of other pathology # (n=3) Normal (n=1)	94% (64-117)	70% (42-86)	72% (38-93)

Summary

- The results of this case series support the model-based prediction that 3 BL BeLPTs can predict BeS and our hypothesis that it can also predict CBD:
 - 4 of 10 workers had BeS and
 - 2 had CBD.
 - 2 others had GLD without other identified cause.
 - 4 had no evidence of BeS, CBD, or GLD.
- No distinguishing differences were noted between CBD, BeS, and GLD groups in regard to demographics, exposure, radiographic abnormalities, or baseline PFTs.
- Greater decline in DLCO after diagnosis was observed in the CBD group.
- 3 BL BeLPTs (without any AB) is an uncommon result pattern (~ 0.04%).

Conclusions

- 3 BL BeLPTs can predict BeS and CBD.
- The decline in DLCO after CBD diagnosis suggests that 3 BL BeLPTs can predict clinically significant disease.
- Beryllium-exposed workers with 3 BL BeLPTs warrant medical evaluation for CBD, like workers with BeS.
- 3 BL BeLPTs is not a commonly observed pattern, suggesting probable BeS and CBD in the two beryllium-exposed workers with 3 BL BeLPTs and GLD, rather than sarcoidosis.

Three Borderline BeLPT's is a Rare Event

- Warrants follow-up
 - NJH recommends clinical evaluation
 - Other options include continuing medical surveillance, split samples
 - Other entities considering 3 BOR as confirming beryllium sensitization
 - American Thoracic Society
 - Washington State Workers Compensation (L&I)
 - “OSHA finds that multiple, consistent borderline BeLPT results (as found with three borderline results) recognize a change in a person's immune system to beryllium exposure”

From the Rule Jan 2017

Future Directions

- Identify workers with three BOR, follow-up
 - Repeat BeLPT Testing
 - Clinical Evaluation
- Follow-up on workers with three BOR who went on to clinical evaluation
 - Repeat clin eval for evidence of progression
- DOE does not currently recognize 3 BOR, this may be addressed in the CBDPP amendment

Summary

- Predictive value of 3 BL BeLPTs approaches 2 AB.
 - Prevalence $\geq 2\text{-}3\%$
- 3 BL BeLPTs can predict BeS and CBD.
- 3 BL BeLPTs is not a commonly observed result pattern.
- We consider 3 BL BeLPTs probable BeS and recommend clinical evaluation for CBD.

Questions?



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